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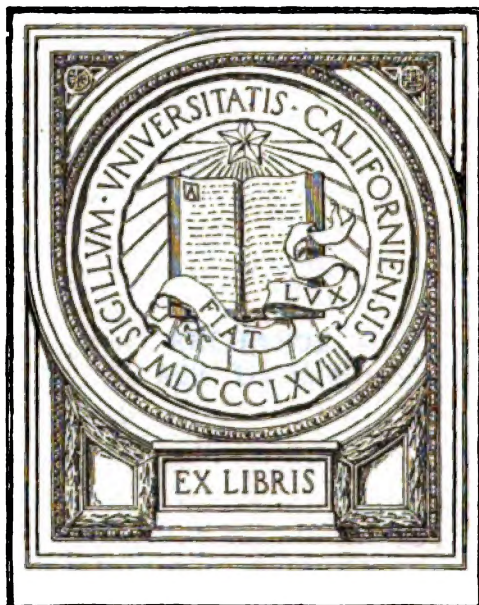
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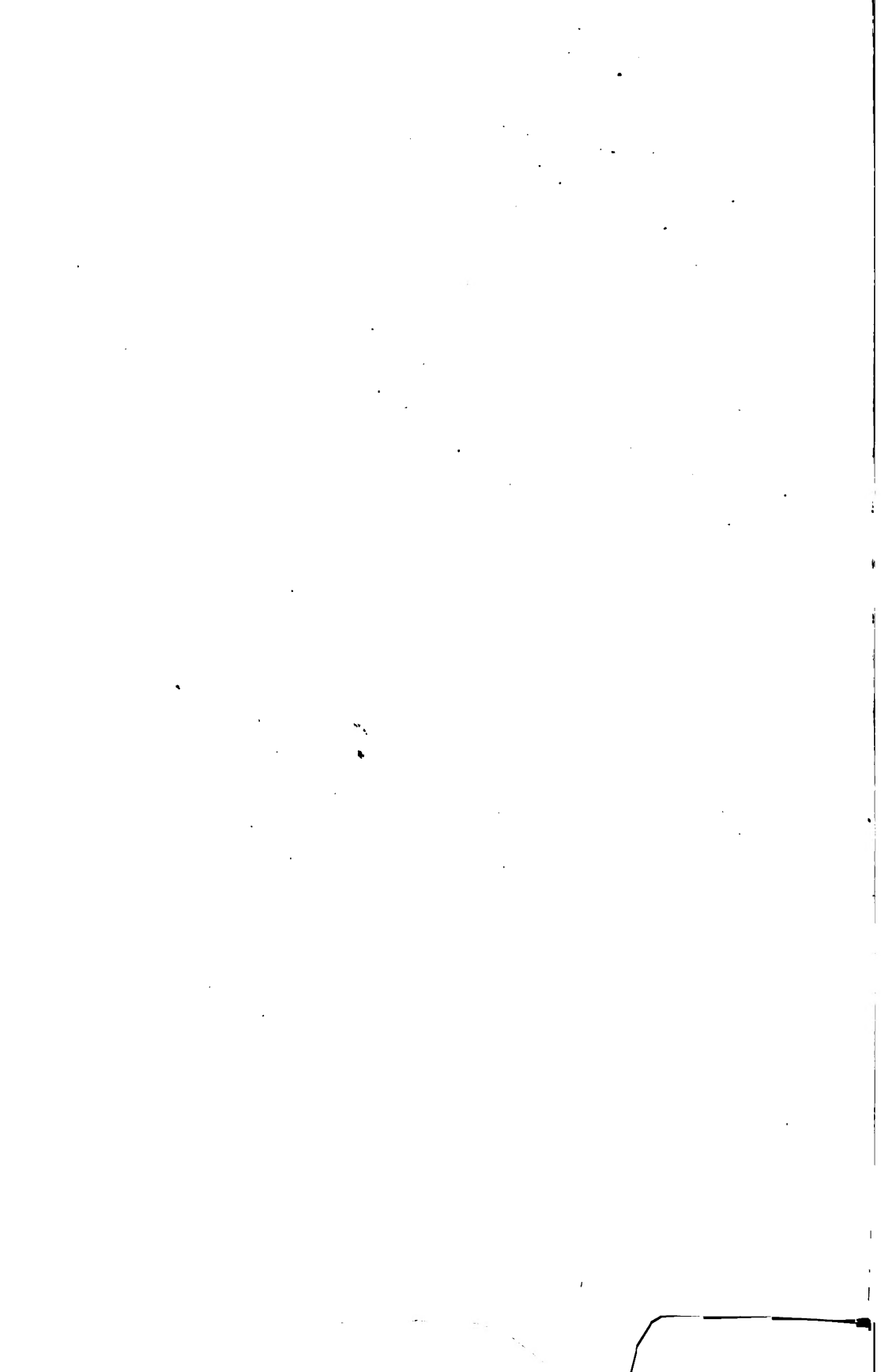
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EDITED BY  
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## THE RELATIONSHIP BETWEEN TONSILLAR INFECTION AND RECURRENT VOMITING\*

R. TAYLOR

The striking features of typical attacks of recurrent vomiting, their periodicity, the prostration and intoxication accompanying them, no less than the prompt cessation of symptoms and the rapid recovery of the patient, have, for twenty years, received much attention from the clinic and the laboratory.

Griffith, in 1900, reported the presence of acetone in the urine of one patient during the attack. This finding was confirmed the next year by Valagussa. Marfan then wrote describing the symptoms of the disease, and its constant association with acetonuria, but considered that the acetone was merely the companion of other toxic and more truly pathogenic substances as yet unknown. Marfan further pointed out that in recurrent vomiting the acetonuria was not due to starvation, as in some instances it was present before the patient had refused food. Howland and Richards concluded that while the presence of acetone bodies could not be considered as owing to carbohydrate starvation, they might well be dependent on insufficient combustion of ingested carbohydrates. They formulated the theory that insufficient oxidation processes were in part responsible for the symptoms, and supported this by the finding in the urine, during the attack, of increased amounts of partially oxidized substances, neutral sulphur, lactic acid, and uric acid. Sedgwick's finding of large amounts of creatin in the urine of children during the attack may also be explained as indirectly due to diminished oxidation.

That the acetone bodies are not in themselves the cause of the symptoms was finally and conclusively shown by Mellanby, who, in 1911, withdrew carbohydrates from a child subject to recurrent vomiting and produced acetonuria, but did not produce vomiting; nor are the attacks due to dietary indiscretion, to indigestion, or to biliousness in the old

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sense. The majority of opinion of those having the largest experience with the disorder has been voiced by Marfan and by Abt, each of whom states that diet during the interval has no effect on the occurrence of the attack.

It is difficult to conceive that a metabolism which functions perfectly for a period of months will then suddenly become subverted and turn out incompletely oxidized toxic products without there being present some cause which was not active during the interval. Sedgwick was the first to lay the responsibility for the attacks of vomiting directly at the door of infection, when, in 1912, he reported eight cases, in all of which the patients were either entirely cured or much improved by the removal of adenoids or tonsils. He also reviewed the literature to that date, finding evidence of infections, sore throat, arthritis, coryza, epistaxis, etc., in the older reports and studies on recurrent vomiting.

My own experience in Dr. Sedgwick's clinic led me to believe that in most of these cases infection of the lymphadenoid tissues in the nasopharynx was an important etiologic factor, and, after beginning work in the Mayo Clinic, I continued to view these cases as possible results of tonsillar or adenoid infection.

Because of the criticisms aimed at wholesale slaughter of tonsils and adenoids, and in order to satisfy myself of the validity of considering the presence of recurrent vomiting as an indication for the removal of tonsils and adenoids, I have studied the case records of the 47 patients treated in the Mayo Clinic previous to the close of the year 1917, and in whom a diagnosis of recurrent vomiting of childhood had been made. Many of these were severe cases. In most instances the children had been brought to the Clinic, often from long distances, in the hope of obtaining relief from the attacks. On the whole, the patients would seem to be representative of the typical form of the disease. Their average age on coming to the Clinic was about seven years; the average age at onset was about three years. The attacks lasted for from one day to two weeks, with an average duration of three or four days; their frequency varied from 3 or 4 to 20 or more a year. In 8 instances the attacks were associated with abdominal pain, usually dull and indefinite. Appendectomy had been performed in 3 instances and appendectomy and cholecystostomy in one, without relief of the symptoms. Septic tonsils, or enlarged infected adenoids, or both, were present in 40 of the 47 patients; 4 of the remaining 7 had hereditary lues; 2 of these had had their tonsils and adenoids removed elsewhere without benefit, and one im-

proved under specific treatment. One of the patients with hereditary lues had small, non-septic tonsils and adenoids, while the record of the fourth contains no mention of the nasopharynx. Of the remaining 3 patients, 2 with mild infrequent attacks had small, apparently normal tonsils and adenoids, while the third, a brother of one of the two, had had his tonsils and adenoids cleanly removed elsewhere, without benefit. Both this patient and his sister were of the neurotic type, and had had severe eczema in infancy. The removal of tonsils and adenoids was advised in 32 of these patients. The remainder were sent home with tonic prescriptions, advice as to diet, laxatives, and general hygiene. The tonsils and adenoids were removed in 24 instances. The basis for this paper is found in the results of operation in these cases, as developed by the replies to the questionnaire mailed to the parents of each patient as follows :

1. Has your child continued to have attacks of vomiting since the tonsils and adenoids were removed here?
2. How many vomiting attacks has your child had since the tonsils and adenoids were removed?
3. Have they been as severe as before the operation?
4. How long do the attacks last at present?
5. Are the vomiting attacks accompanied by severe abdominal pain?

No reply was received in 6 instances. The parents of one child who, at operation two years previously, was four years old, and having annually about four attacks of from one to two days' duration, report that he now has about five attacks annually, each about three or four days long and not accompanied by abdominal pain. Of the remaining 17 patients, one who was having five or six two- to four-day attacks each year had had two attacks of one day each in the ten months since operation. One parent, one year after operation, reports that the child is much improved. Another child who had monthly attacks has had only three short ones, with an average duration of fifteen hours, in the three years since operation. These attacks have been accompanied by abdominal pain. One patient had had a few severe attacks shortly after the operation, with two attacks, each lasting only a half day, in the last year. This patient was operated on four years previously at the age of nine years, when she was having about ten one- to five-day attacks each year. One other patient, a nine-year-old boy who, one year ago, was having more than two attacks a month, has had three in the ten months



since operation, and these have been mild and have lasted less than one day. The remaining 12 patients have had no further attacks.

TABLE 1.—PATIENTS OPERATED ON

NUMBER	AGE	AGE AT ONSET	ABDOMINAL PAIN	DURATION, DAYS	SYMPTOM*	FOCUS*	TONSILS AND ADENOIDS PREVIOUSLY REMOVED	TONSILS AND ADENOIDS REMOVED	RESULTS
190245	7	Early	0	2-3	15 a year	Tonsils 3; adenoids 2	0	+	No answer.
197311	5	Early	0	3-4	3-4 a year	Tonsils 3; adenoids 3	0	+	No attacks in year following operation.
200248	7	6	0	1-2	6-10 a year	Tonsils 2; adenoids 1	0	+	No answer.
200492	4	2	0	4-5	3 a year	Tonsils 3; adenoids 2	0	+	No attacks in eleven months following operation.
201571	8	2	+	2-4	5-6 a year	Tonsils 3; adenoids 2	0	+	Two attacks lasting one day in ten months since operation.
128926	4	...	0	2	12-15 a year	Tonsils 3; adenoids 3	+	+	Much improved in the first year after operation.
138053	5	...	+	1	12 a year	Tonsils 2; adenoids 1	...	+	Two attacks in three years since operation. Attacks accompanied by abdominal pain.
140273	10	5	...	3-5	4 a year	Tonsils 3; adenoids 2	...	+	No attacks in three years since operation.
168615	15	4	0	2	3 a year	Tonsils 3; adenoids	0	+	No answer.
170853	4	2	+	1-2	4 a year	Tonsils 2; adenoids 2	0	+	Continues to have 4 or 5 attacks a year.
174799	6	3	0	3 or more	Many	Tonsils 3; dental caries	0	+	No attacks in eighteen months since operation.
175216	5	...	...	...	2-3 a year	Tonsils 2; adenoids 1	0	+	No attacks in eighteen months since operation.
176002	9	2	0	3-5	4-6 a year	Tonsils 3; adenoids 2	0	+	No attacks in nineteen months since operation.
115185	9	6	0	1-3	8-10 a year	Tonsils 4; adenoids 3	0	+	No severe attacks in four years since operation.
119817	7	2	0	2-3	12 a year	Tonsils 3; adenoids 3 Mother has lues	0	+	No attacks in fifteen months since operation.
206600	9	2	0	1	Every week	Tonsils 2; organic heart	0	+	Three attacks in ten months since operation.
205073	3	...	0	2	15-20 a year	Tonsils 3; enlarged glands; adenoids; pyelocystitis	0	+	No answer.
205685	2 1/2	...	0	1	3-4 a year	Tonsils 3 with glands	0	+	No attacks in ten months since operation.
176074	5	16 mos.	0	5-6	4 a year	Tonsils 3	0	+	No answer.
201575	7	...	0	4-5	6 a year	Tonsils 2; adenoids 2	0	+	No answer.
219441	6	3	0	2-14	Many	Septic tonsils with adenoids	0	+	No attacks in five months since operation.
64611	5	3	0	1-3	4-20 a year	Large tonsils and adenoids; father has lues	0	+	No attacks in six years since operation.
212776	8	...	0	7	3-4 a year	Large septic tonsils and adenoids	0	+	No attacks in seven months since operation.
190162	7	5	...	2-7	4-5 a year	Tonsils 2; pyuria	0	+	No attacks in one and one-half years since operation.

\* Tonsils and adenoids are arbitrarily graded as to the degree of hypertrophy on a scale of 1, 2, 3, and 4. Tonsils 2, adenoids 1, represent the findings in the usual child's pharynx. This grading does not measure accurately the pathology present.

To summarize the evidence obtained from these records of 47 cases of recurrent vomiting, we find that in 40 there was evidence of tonsillar

or adenoid disease. In 6 of the 24 patients whose tonsils and adenoids were removed no further information could be secured. One of the remaining 18 patients is unimproved. Five are very much improved, and 12 have had no attacks since operation, this period varying from seven months to six years.

TABLE 2.—PATIENTS NOT OPERATED ON

NUMBER	AGE	AGE AT ONSET	ABDOMINAL PAIN	DURATION, DAYS	FREQUENCY	FOCI OF INFECTION	TONSILS AND ADENOIDS PREVIOUSLY REMOVED
158678 188574	6 11	4 Early	.. +	2-3 1-2	Many 10-12 a year	Tonsils 2; remaining adenoids 1 Tonsils 2; adenoids 1	+ 0 Appendix removed at 9 years.
188876 140055	11 7	9 3	.. +	.. 2-3	Many 30-40 a year	Tonsils 3; adenoids 1 Tonsils 4; adenoids 3	0 0
188739 169457	7 9	3 7	0 0	2-5 1-2	4-6 a year 12-15 a year	Tonsils 3; adenoids 2 Tonsil stumps 2; dental caries and adenoids	0 At 5 years
205876	12	..	..	..	Occasional	Tonsils 2; adenoids 1. Chronic otitis media	0
109245 207117	9 12	5 1	0 0	1-2 3-4 wks.	4 a year 6-8 a year	Hereditary lues Hereditary lues	+ + No improvement.
204142	16	6	+	3-4	4-8 a year	Hereditary lues. Non-septic tonsils	Appendectomy; cholecystostomy; no relief.
94461 214110	3 4	2 ..	.. 0	3-4 ..	4 a year Occasional	Mother has lues Large tonsils with adenoids	0 0
204976 209252	6 9	3 Infancy	0 0	1 3-5	Occasional Every 3-4 wks.	Tonsils 1; adenoids 1 Tonsils 3; adenoids 1; mild chorea	0 0
210779	3	2	0	Several	Every few wks.	Tonsils small, slightly septic.	0
211990	8	..	0	Few	Occasional	Colds and sore throat Small non-septic tonsils and adenoids	0
179002	12	10	0	1	1 a week	Tonsils 2; adenoids 2	Appendectomy one year previously; no benefit.
204886 66819	11 4	6 3	0 0	2-7 7-14	Frequent 6 a year	No tonsils and adenoids Large tonsils. Operative adenoids	+ No improvement.
72682	6	2	+	2-4	4 a year	Medium-sized tonsils and adenoids. Pus and casts in urine	..
75459	9	5	0	1	Every 2-3 wks.	Medium-sized tonsils, large adenoids	0
82204 100502	9 5	Infancy 5 mos.	0 0	1-3 2-6	Every 2-3 wks. Every 2-3 mos.	Repeated tonsillitis Tonsils 2; adenoids 2	0 0

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## THE ARTIFICIAL FEEDING OF INFANTS\*

R. TAYLOR

In 1916 Dr. Sedgwick presented before this Association a discussion on the subject of breast-feeding which, I am sure, is here, as it is elsewhere, a far more important topic than that of artificial feeding, on which your secretary has requested me to speak.

The conditions in Montana, with practically no congested slum districts, the people living largely in small communities, are very different from those in centers like New York, where large numbers of babes with no mothers have to be cared for. Even in Minneapolis, where I formerly cared for large numbers of babes from poor parts of the city, in the Infants' Welfare Clinics, artificial feeding from the outset was the exception. The principle which I am sure Dr. Sedgwick presented to you, that practically all women, save those with open tuberculosis, can supply, if not the whole of their infants' needs, at least a considerable portion of it in breast milk, and that this supply can be maintained by suitable stimulation of the breast, for at least a number of months, holds true always. I have never had under my care a nursing babe whom I have had to take off the breast within the first few months. The problem of artificial feeding, as it comes to me, concerns, first, a small number of foundlings and babes whose mothers have cancer of the breast or pulmonary tuberculosis, and who have to be bottle-fed from the outset. The greater portion of them, however, are babes two, three, or four months of age, who have had the breast for a short period of time, but who were weaned, either because they themselves did not nurse vigorously and stimulate the mother's breasts or because they were crying or fretful, or passed green, frequent stools, and it had been erroneously supposed that the breast milk was at fault.

There are no systems of infant-feeding, any more than there are systems of medicine. Percentage feeding, so largely employed in Boston and Philadelphia, is only a method of reckoning the relative amounts of

\* Presented before the Montana State Medical Association, July 10-11, 1918, at Butte. Reprinted from the *Journal-Lancet*, 1918, xxxviii, 433, 435.

the different food-stuffs given to the infant. The foods taken well by one infant will not be suitable for another; and, no matter how the formula is reckoned, the underlying principles are, first, that the infant must be fed food which he tolerates both in quality and quantity, and, second, that the relative proportion of the food-stuffs—fats, proteins, and carbohydrates—must be adapted to the infant's physiologic ability and needs.

Cow's milk forms the basis of all artificial infant foods. It contains the protein casein, the carbohydrate lactose, or milk-sugar, fat, and the soluble whey proteins, and salts. Protein taken into the intestine brings forth alkaline digestive juices, and, when it reaches lower intestinal levels and becomes subject to bacterial action, undergoes a certain amount of putrefaction with the production of alkaline end-products. Carbohydrate, on the contrary, undergoes fermentation with the production of acid. Lactose, for example, may produce lactic acid. Fat is split in the stomach and intestine, as you know, into fatty acids and glycerin. The further fate of the fatty acid depends upon whether the surrounding medium is alkaline or acid, this reaction depending, as I have before stated, on the relative proportion of protein and fermentable carbohydrate in the food. If alkaline, the fatty acids unite with the bases calcium and magnesium to form soaps. These soaps are not irritating, peristalsis is not hastened, and the babe tends to be constipated. If, on the contrary, the sugar content of the food is high and acids predominate in the intestine, the fatty acids remain unneutralized and stimulate peristalsis, provoking more frequent stools, or diarrhea.

Let us consider the case of a babe three months old, brought in without a history, and for whom it is impossible to obtain breast milk. The first problem is to determine the babe's tolerance. I do this in the following way:

I know that a normal babe of that age will, as a rule, take in the neighborhood of about 15 ounces of whole milk daily, provided it is properly diluted. I also know, from experience, that a healthy babe of that age takes milk which is diluted with an equal amount of water, so that without hope of achieving a gain in weight, I order for that babe about 5 ounces of half milk and half water, to be given five or six times in the twenty-four hours, and tell the mother to return in two or three days. This is done simply to determine the babe's ability to tolerate one-half milk. If when the mother returns with the babe I find, as I supposed, that it is not only hungry but constipated, I then make a

carbohydrate addition. Ordinarily at this age the addition consists of about one tablespoonful of barley flour. Then, if the babe is constipated, but does not gain, further carbohydrates may be added. Usually I add some form of sugar, either cane sugar or lactose, or one of the mixtures of maltose and dextrin that are on the market.

As regards the amount of milk needed by these babes, it will usually be found that the babe will thrive on about one-tenth of its body-weight in milk a day, and as regards the amounts given at separate meal-times, approximately two ounces more are given than the babe is old in months. It so happens that such an amount of milk and water furnishes about 70 calories per kilo of the babe's weight per day. Most artificially fed babes will not gain on that quantity of food, and it is only when the lacking 30 to 40 calories per kilo are made up by carbohydrates that gain in weight recommences. I have purposely left the question of calories until I have begun with this concrete example of a feeding case, because I feel that one should use his knowledge of the energy content of various foods as expressed in calories, not as a method of feeding, but as a method of checking, in order to determine reasons for gain or failure to gain.

Let us return to our three-months-old babe, and let us suppose that, when the mother came back two days after I had first seen her and put the babe on his 5 ounces of one-half milk and one-half water every four hours, she had brought with her a diaper containing a slimy, green stool, containing small, white or grayish masses and had told me that the babe was passing five and six stools daily, showed me the babe's red buttocks, and further stated that the babe was crying and fussy all the time, I would know beyond question that the food he was given was beyond his ability to tolerate. And because the mixture had already contained a minimum amount of milk and had contained no added carbohydrate. I would know that, for the present at least, it was impossible to feed that babe with the simple milk mixture. I would then give protein milk. Protein milk was originated by Finkelstein under the name of "Eiweiss" milk, and, in the hands of many men throughout this country, it has proved its worth over and over. It is made as follows:\*

"1 quart milk.

Digestive ferment.

1 pint buttermilk.

2 level tablespoonfuls wheat flour.

1 pint water.

Dextrimaltose as directed.

\* Abt, I. A.: The baby's food. Philadelphia, Saunders, 1918, 37-38.

**“Heat 1 quart of fresh whole milk to 98° to 100° F., then add 2 level tablespoonfuls chymogen powder or essence of pepsin (1 teaspoonful) or a junket tablet (previously dissolved in a little cold water); place in a water-bath of 107° F. for fifteen to twenty minutes until coagulated; and then hang in a sterile muslin bag one hour to drain off the liquor of the milk.**

**“To the curd of 1 quart of milk thus obtained add 1 pint of buttermilk, and rub through a copper hairstrainer three times. To this add 2 level tablespoonfuls of wheat flour rubbed to a paste with 1 pint of water. Boil the mixture ten minutes, cutting back and forth constantly, not stirring, with a large wooden spoon; otherwise large curds will form. If necessary add water to make the finished mixture 1 quart.**

**“Dextrimaltose (3 to 5 per cent) should be added when directed by the physician. The early addition of 3 per cent of dextrimaltose is advisable. This is best done by dissolving the dextrimaltose in a moderate quantity of water and adding while the mixture is boiling. The albumin milk must not be overheated before feeding, as it will curdle.”**

You will note that the mixture is rich in protein, moderately rich in fat, and poor in carbohydrate. Alkaline intestinal contents, soap stools, and constipation should, and do, result from its use. Furthermore, its salt content is relatively low, a factor which may be of great importance. Its production entails a certain amount of work on the part of the mother or nurse, but either can be taught to make it successfully. A knowledge of the manner of preparation and the indications for its use cannot but be among the most valuable possessions in the doctor's therapeutic armamentarium. I have tried skimmed milk and buttermilk, starch solutions, and evaporated milk, but when a babe has diarrhea of purely alimentary origin, when it can take no other artificial food, the chances are that by the use of protein milk the babe can be fed and kept constipated. We will suppose, then, that the mother is instructed in the use of protein milk, told to put the babe on the 5 ounces five times a day with an addition of 3 per cent of carbohydrates, which I make in the form of Mead's dextrimaltose, usually she is apt to return with the news that the babe is constipated, and then we will cautiously increase the amount of dextrimaltose, raising it from 3 to 5 and 7 to 9, 10, or even to higher percentages, such as 12, with protein milk. As long as the babe remains constipated and is not gaining sufficiently, it is safe to make these carbohydrate additions; and by them one will nearly always eventually secure, not only a gain in weight, but also a plump, firm, solid infant.

Some weeks, and even months, later, when the babe has increased his tolerance for food, the protein milk may be stopped, and a milk mixture suitable to the babe's needs may again be tried.

Let us return once more to the day when the mother comes back to the office after having her babe on the diluted milk for two days. We will suppose that, instead of diarrhea, the story is of vomiting. Such cases are rarer than the one I have just presented. But when this is the case, when the babe's trouble is that he vomits and fails to gain on the diluted milk, the best artificial food I have found is the old-time Holland mixture of buttermilk, flour, and sugar, with which you are all, no doubt, more or less familiar. A few babes begin to vomit on this, and when they do it has to be discontinued. But in general this food, which is largely a carbohydrate one, is well tolerated by the infant's stomach, and with it a fine gain in weight, a comfortable babe, and a pleased mother may be obtained. If the babe has diarrhea on this, I try the protein milk. The buttermilk mixture should not be continued for a great length of time. In common with mixtures containing large amounts of carbohydrates, such as the sweetened condensed milks, Imperial Granum, etc., its continued use leads invariably to anemia, to rickets, and to lessened resistance to infectious diseases. In general, I use only these three classes of bottle mixtures for the healthy young infant. Boiled whole milk diluted with cereal gruel or with sugar solution, or both, protein milk with from 3 to 12 per cent of dextrimaltose and buttermilk, made up with from 1 to 3 tablespoonfuls of flour and 2 to 4 tablespoonfuls of sugar to the quart. At the present time in New York City the unsweetened evaporated milks are employed a great deal in feeding babes who do not tolerate simple dilutions. I have tried evaporated milk, and have found it to work well in some cases, but I do not think, on the whole, it is as good as the protein milk, its advantage being that it is more easily prepared. I must again emphasize that the feeding of each individual babe is a problem in itself, that one can lay down no empirical rules, saying, for instance, that all artificial feeding of babes should begin with one-third milk and two-thirds 8 per cent sugar solution, or that it should begin with 3 per cent of fat, 6 per cent of carbohydrate, and 1 per cent protein. But, nevertheless, one does employ a sort of rule of thumb basis for his calculations. If the babe is normal,—by that I mean that its weight is approximately the average for its age, that it has been born at term, and that its parents must have been neither too young nor too old,—it is usually safe to start

out in the first month with a proportion of 1 part of milk to 2 of water, and in the second and third months, with equal amounts of milk and water, and after the first four or five months to employ, instead of one-half milk and one-half water, a mixture of two-thirds milk and one-third water as a starting-point. Regularity of feeding-time is much more necessary in artificial feeding than in breast-feeding. My own experience leads me absolutely to favor the four-hour interval with no more than five or six feedings in the twenty-four hours for the artificially fed babe. When its food is tolerated and is physiologically adapted to the infant, I have been able to show that hunger, as evidenced by the gastric contractions, does not become intense until the end of the four-hour period. On the contrary, in babes who were being fed every two or three hours, who were receiving more food than they could tolerate, hunger occurred at the end of one and one-half hours, and two hours, often before the stomach was emptied. This coincides with the clinical observations that the fussy, crying babe is more apt to be overfed than underfed.

Increases in the amount of food given the babe should not be made simply because it cries, nor should they be made if the babe has more than two or three loose stools daily. Increases should not be made as long as the babe is making a satisfactory gain in weight. The amount needed by the infant gradually increases during the first six months, and, if the amounts of a well-tolerated food are not increased, the weight will come to a standstill; therefore, the best method is to watch the babe's weight, the stools and their character, and, if possible, the temperature. This latter, which is always between 98° and 99° in a normal young infant, becomes irregular if food is not tolerated. When, however, the weight curve flattens out in a babe who is receiving a well-tolerated food and who is apt to be passing fewer stools than before, an increase in the amount of food is indicated. Increases should be made gradually. At the end of the first month one can go from 3 ounces of one-third cow's milk with 8 per cent sugar solution, to 3 ounces of one-half milk and one-half 10 per cent sugar solution. About the second month, usually, the amount per feeding may be increased to 4 ounces, and in the third month to 5 ounces. At about this time a cereal solution, such as barley water in addition to the milk and sugar, may be employed. In the fourth and fifth months usually three-fifths or two-thirds milk may be used. Orange-juice should be given daily to these babes after the second month. In the sixth or seventh month I begin giving a thicker cereal, usually



the same one with which the mother is diluting the milk; then I add zwieback, rusks, or toast, then vegetable soup, vegetables, fruit pulp, and at the end of the first year a little scraped beef. These increases are made slowly, the principles being that a new food should be used in only teaspoonful quantities, and that two new foods shall not be begun on the same day. In general, during the second half year the babe takes about 24 ounces of milk, with fruit, cereal, and vegetables, in gradually increasing amounts.

It is difficult to speak on artificial feeding of the normal infant because the transition between health and intestinal disease in the unnaturally fed infant is gradual. Certainly, all bottle-fed young infants should be treated prophylactically, and only by having them seen and studied by the doctor at regular intervals can they be kept approximately safe.

## ESOPHAGEAL DIVERTICULA\*

E. S. JUDD

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Dilatations of the entire esophagus are usually produced by spasmodic contractions at the lower end, while dilatations involving only a segment of the organ are either congenital or situated above a stricture. These dilatations differ entirely from diverticula in that the former involve all of the structures of the esophagus, while the diverticula are in reality only hernias involving the mucous membrane and submucosa which project through the muscular coats.

The diverticula are divided into two types: traction and pressure diverticula. In traction diverticula the distortion is usually due to a pulling force acting from outside the esophagus, and generally occurs at the point where the esophagus crosses the left bronchus. It is most often due to the contraction of a cicatrix formed by the healing of a suppurating lymph-gland. Diseases in the pleura or lung, adhesions to the thyroid, when there is a marked cystic degeneration, mediastinitis, and caries of the vertebræ, have all been cited as etiologic factors in producing this form of diverticulum. It has also been noted that these diverticula are often multiple. In 1900, Brosch called attention to the cavum broncho-aorticum, stating that the aorta, bending to the left and backward, crosses the esophagus on its left side, forming between the aorta and the left bronchus this narrow space where the esophagus is not in contact with any firm structure, as is the case in other regions. As food passing down the esophagus is presumably under more or less pressure from the surrounding firm structures, there is an opportunity for pouching on its arrival at this point where outside pressure is lacking and internal pressure predominates. LeCount has observed three of these diverticula which were unattached either to lymph-nodes or to any surrounding structure. As no microscopic examinations were made of the sacs in these cases it is uncertain how many of the esophageal coats were in-

\* Presented before the Minnesota Academy of Medicine, St. Paul, February 13, 1918. Reprinted from Surg., Gynec. and Obst., 1918, xxvii, 135-141.

volved. According to the location, size, and other characteristics, these cases might have been classified as traction diverticula but for the fact that there was no pulling from the outside.

Traction diverticula usually produce no symptoms and are of no surgical importance. It is said that the apex of the diverticulum is usually higher than the base, so that no food or mucus can accumulate in it. However, in some cases the apex has been low enough to allow an accumulation of food particles, and these cases are known as traction-pulsion diverticula which sometimes attain to considerable size. Even then they seldom present symptoms. We have seen one case in which there was a fairly large sac at the lower end of the esophagus which apparently produced few if any symptoms (Fig. 14, Case 197786). The findings were as follows:

CASE 197786.—W. T. W., a male, aged forty-two years, consulted us July 14, 1917, at which time he gave a history of stomach trouble of twenty years' duration. He complained chiefly of a feeling of fullness coming on in spells, periodically. There had been no regurgitation of food or sense of obstruction during this period. He had been treated elsewhere for stomach trouble for fifteen years. Five years previously he had vomited a large quantity of dark blood and since that time there had been considerable regurgitation of acid food and mucus. His condition gradually grew worse up to the time of our examination. Two years previous to this he had had an x-ray examination of the esophagus and stomach elsewhere, with a negative diagnosis; at this time he had had two nocturnal attacks of epilepsy, and later, two other attacks. Physical examination showed a fairly well-nourished man weighing 183 pounds. The Wassermann test was negative. The x-ray examination of the stomach was negative, but revealed a diverticulum of the lower third of the esophagus, which confirmed the opinion that had been given.

Tetens found that of 80 traction diverticula, 6 had assumed the characteristics of the traction-pressure variety from the accumulation of food and inside pressure.

The pulsion or pressure diverticulum is a particularly interesting condition and the treatment shows marked development in this kind of surgery in a comparatively few years. Zenker and Ziemssen, in 1877, described such diverticula, and their description of the occurrence and pathology is the basis for all of our present knowledge concerning them. They stated that radical cure of a diverticulum of the esophagus by operative procedure from without was one of our vain wishes, but they hoped that even this operation might at some future day be performed

safely. At the present time this condition can be readily and accurately diagnosed and is amenable to surgical treatment. Such diverticula are always located in the cervical region in the unsupported esophageal wall at a point directly opposite the cricoid cartilage. This is a weak point in the arrangement of the musculature at the juncture of the pharynx with the esophagus, and is sometimes spoken of as the pharyngeal dimple. There is a physiologic narrowing at the level of the constrictor muscle, and a hiatus exists in the longitudinal muscle. In all of our cases this opening has been posterior and the sac has usually presented itself to the left side. Just what the etiologic factor in these pressure diverticula is has never been definitely shown, but it has been shown that the pressure in the esophagus is greatly increased during deglutition. Hirsch has demonstrated that deglutition is buccopharyngeal and esophageal, and that foods are carried down the esophagus by peristaltic contractions. He has also demonstrated that it is necessary for the upper orifice to be closed in order to allow the contents of the esophagus to enter the stomach; otherwise there is regurgitation. It is very likely that this pressure is greater if the food is not properly masticated and is swallowed too rapidly. It is quite possible that any unusual increase in pressure may account for the formation of some diverticula.

About 150 pressure diverticula have been reported in the literature. Several years ago Stetton collected 60 cases in which operation had been done, with a mortality of 16.6 per cent. There are 35 cases in our series.

The first symptoms of the condition are usually dryness in the throat and a scratchy feeling as though there were a small foreign body present. These sensations make it difficult for the person to swallow. Nausea follows; mucus is raised from the throat and later particles of undigested food are brought up. Difficulty in swallowing was noted in all of our cases, and 30 of the 35 patients complained of regurgitation of food. A gurgling noise in the throat, which is often mentioned, was present in 12 of the cases. A feeling of pressure, symptoms of stricture, and choking sensations develop. The symptoms of an esophageal diverticulum rarely present themselves before patients are forty-five years of age. The average age in our 35 patients when they came for treatment was fifty-four years; the average duration of symptoms was five and one-half years. A visible or palpable tumor of the neck occurs only when the sac is large, and in the cases formerly reported this occurred in about 30 per cent. Ten of the patients of our series had a

visible or palpable tumor in the neck. In 7 cases the tumor was on the left side, in 3 on the right. The weight loss is great in case the sac is large or so shaped as to close off the lumen of the esophagus. In some of the cases the obstruction was almost complete.

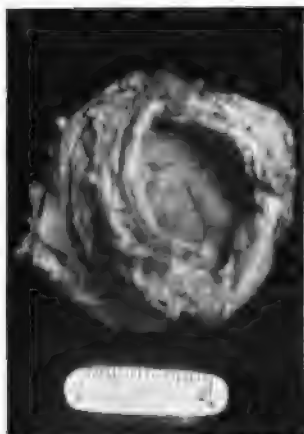


Fig. 1 (116523)

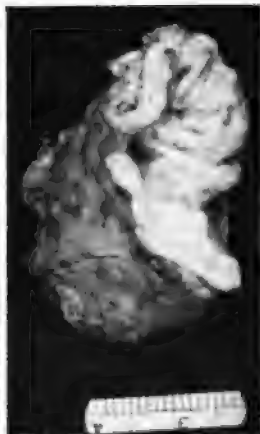


Fig. 2 (194431)

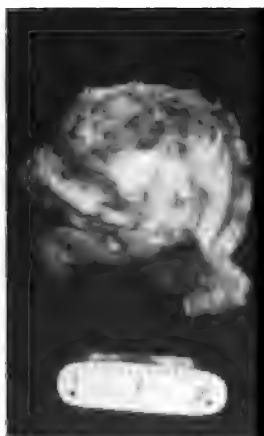


Fig. 3 (91276)

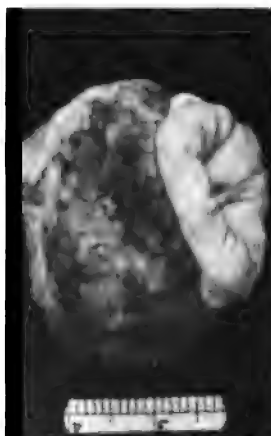


Fig. 4 (183605)

Figs. 1-4.—Photographs of diverticula showing the character of the walls.

The average loss of weight in the entire series was 27 pounds, the highest being 65 pounds. In 8 cases in which the diverticulum was small there was no loss in weight. Some of these patients learn to feed themselves with a stomach-tube when the swallowing becomes too difficult. In some of the extremely emaciated patients it seemed best to perform a gastrostomy before attempting any treatment of the diverticulum, although feeding can usually be kept up with a small tube. I believe preliminary gastrostomy is seldom, if ever, necessary.

The size of the sac of the diverticulum varies greatly. The opening into the esophagus may be small, producing a typical saccular diverticulum, but in some of our cases the opening was as large as the lumen of the esophagus. It is well to bear in mind that in a certain number of these cases the opening

of the diverticulum is large, because in removing them too much of the wall of the esophagus itself may be removed (Figs. 1-12).

The diagnosis can practically always be made by means of an x-ray picture, taken after swallowing a bismuth mixture. The x-ray and the esophagoscope make the diagnosis certain. The history nearly always gives a good clue to the diagnosis, and this, together with a physical examination and the presence of the characteristic swelling in the neck, is sufficient. Before the use of the modern methods of examination many of these cases were diagnosed as cardiospasm, esophageal stricture, and carcinoma. In many instances gastrostomy has been performed for esophageal diverticulum on the assumption that the obstruction was caused by malignancy.

The treatment of esophageal diverticula is surgical and should be made as conservative as possible. It consists in either obliterating or removing the sac, several different methods having been devised for this purpose. In the extreme cases it is always necessary to put the patients into as good general condition as possible before attempting any treat-

ment for the diverticula. Instead of performing a preliminary gastrostomy, as has been suggested in the emaciated and starved cases, the same object can often be accomplished by rectal feeding, subcutaneous salines, and feeding with a stomach-tube when that is possible. The majority of our patients came for treatment in a sufficiently satisfactory general condition to warrant doing the operation on the diverticulum without any preliminary measures.

When the diverticulum is small and has a large opening communicating with the esophagus, dilatation with large sounds will, in some instances, relieve all the symptoms, while in others this method of treat-

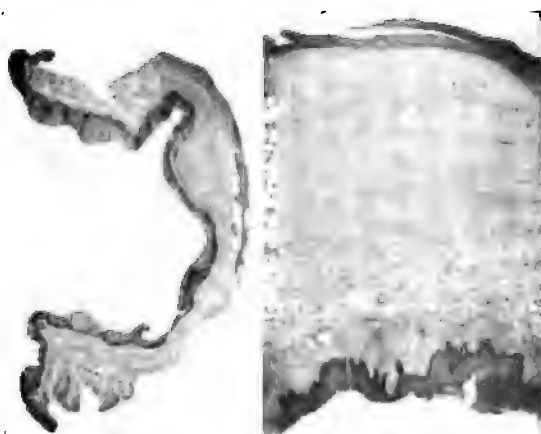


Fig. 5

Fig. 6

Fig. 5 (85020) (at left).—Low-power photomicrograph of cross-sections, showing the walls of the diverticula made up of mucous membrane and submucosa.

Fig. 6 (206243).—High power of cross-section of a diverticulum. (See Fig. 5.)

ment may be preferable to the more radical excision, especially if there

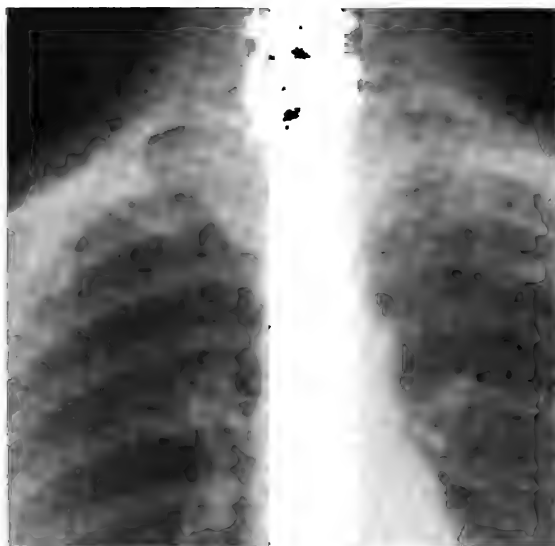


Fig. 7 (23253)



Fig. 8 (23253)

Figs. 7 and 8.—X-ray photographs of small esophageal diverticula.

is any contraindication to the open operation. Mixer has satisfactorily treated a number of patients in this way; however, it might be necessary to repeat the treatment from time to time.

Bevan recently described a method of infolding the diverticulum by means of a series of purse-string sutures, and reported a number of cases in which the results were very satisfactory. By this method the sac itself is not removed, but is gradually folded up and turned into the lumen of the esophagus, where it either atrophies or is cast off. Girard has cured two patients by this method. This operation has the great advantage of eliminating every possibility of infection, as the mucous membrane is not

opened. The sac is composed only of mucous membrane and submucosa, and the operation is usually easily performed. The element of

infection is very important in these cases, and when the esophagus is opened, it is sometimes difficult to prevent a small amount of soiling.

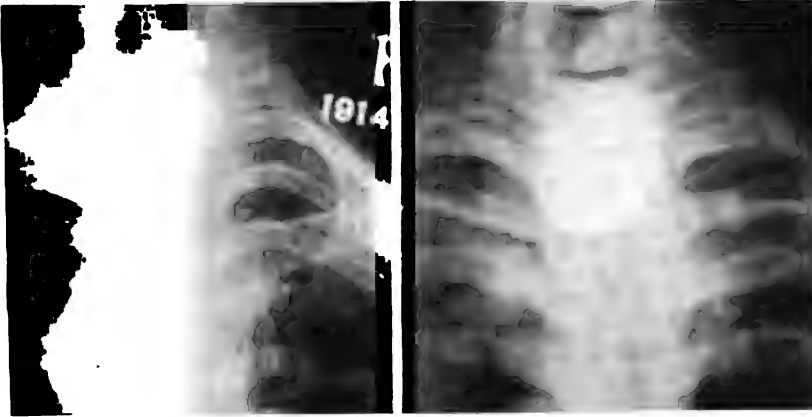


Fig. 9 (91431)

Fig. 10 (99356)

Figs. 9 and 10.—X-ray photographs of medium-sized esophageal diverticula.

The tissues of the esophagus tear very easily, and even if the sutures are accurately placed in the cases in which a complete excision is done, the movements caused by swallowing may produce a small opening between

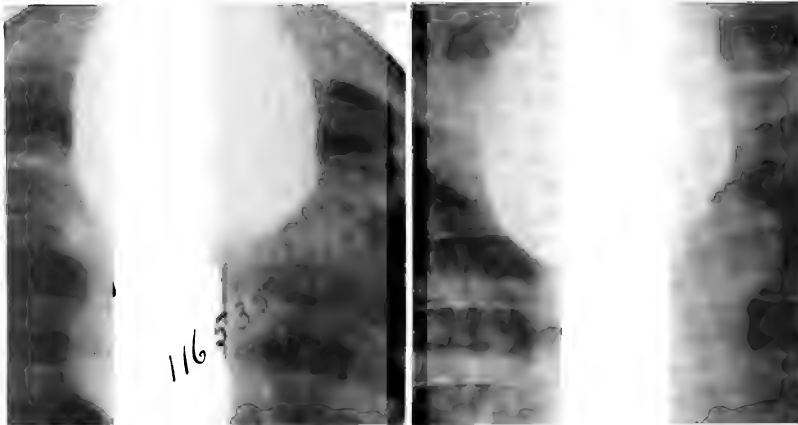


Fig. 11 (116535)

Fig. 12 (8889)

Figs. 11 and 12.—X-ray photographs of large esophageal diverticula projecting into the mediastinum.

the sutures. This drainage from the esophagus naturally passes down the anterior surface of the vertebræ into the mediastinum and may result



very seriously. For this reason whenever the infolding operation, as described by Bevan, can be performed, it certainly is the operation of choice. This method can be employed in the cases of the smaller sacs and in those in which the sac is of medium size, but if the diverticulum is very large and reaches down into the thorax, it would seem that it is preferable to employ the two-stage operation as devised by C. H. Mayo. Murphy described a two-stage operation for all cases. The first stage consists in dissecting the sac out of the surrounding tissues, twisting it, and suturing it in this position and allowing granulations to form about it for from twelve days to two weeks, before removing it at a second

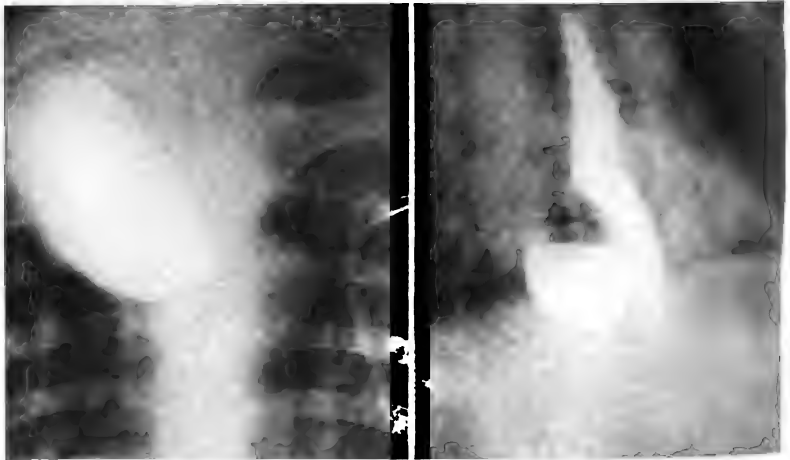


Fig. 13 (2492)

Fig. 14 (197786)

Fig. 13.—Shows the communication of the diverticulum with the esophagus to be apparently lower than usual. This is probably due to the fact that the sac is not completely filled.

Fig. 14.—X-ray photograph of a large diverticulum at the lower end of the esophagus. Note abstract of history.

stage. The method, as employed by Mayo, is first to dissect the large sac out of the thorax, leaving the neck attached without opening the sac during the first stage. After it is entirely freed, the wound in the neck is sutured and the sac left outside of the neck in the dressing. The skin edges are sutured to the esophagus at its juncture with the diverticulum. After ten or twelve days adhesions have formed about the sac and it can be removed without an anesthetic and the edges turned into the esophagus. This operation is not difficult and is perfectly safe from any possibility of infection; it has been very satisfactory in our cases in which the sac was fairly large (Figs. 15 and 16).

TABLE 1.—ESOPHAGEAL DIVERTICULA

Diverticulum of the esophagus (6 cases previously reported by Dr. C. H. Mayo).....	35 cases
Males.....	28 cases
Females.....	7 cases
Average age.....	54 years
Average duration of symptoms.....	5½ years
Difficulty in swallowing.....	35 cases
Regurgitation of food.....	30 cases
First symptoms noted:	
Difficulty in swallowing.....	13 cases
Gurgling noise in the throat.....	12 cases
Regurgitation of food.....	8 cases
Choking sensation.....	2 cases
Tumor of the neck visible or palpable (left side 7; right side 3).....	10 cases
No loss of weight in.....	8 cases
Loss of weight in.....	19 cases
Average loss.....	27 pounds
Greatest loss.....	65 pounds
Weight not given in.....	8 cases
X-ray diagnosis of diverticulum of the esophagus in.....	24 cases
X-ray examination one month after operation showed the esophagus to be negative in.....	4 cases
Bevan operation.....	1 case
Excision of the sac and inversion of the base.....	1 case
C. H. Mayo two-stage operations.....	2 cases
Size of the sac 1 to 4 ounces, noted in.....	16 cases

In operating, the approach was from the left side of the neck in all except one case, and that was from the right side. In 6 cases a transverse incision was made. One patient had been operated on for diverticulum one year before coming to the clinic. There was recurrence in one case. The patient began to have trouble about one month after operation and was operated on nine months later by the two-stage operation. This was the only recurrence in the series.

TABLE 2.—TYPES OF OPERATION

The sac was excised and the base inverted in.....	18 cases
The sac was excised and the base ligated and turned in.....	4 cases
The Bevan operation was done in.....	3 cases
The two-stage operation (C. H. Mayo) was done in.....	10 cases

There were two deaths following operation, both on the second day. Both patients were known to be poor surgical risks—one a male aged seventy-six years, the other a male aged seventy-three years. The cause of death in both instances was cardiac disorder. One died after the first of a two-stage operation; one after excision of the sac and inversion of the base.

The infolding operation in the case of small diverticula and the two-stage operation for large diverticula seem to be very satisfactory and safe methods of procedure in all cases of diverticula of the esophagus.

The results from these operations are very gratifying, as almost every patient thus operated on has been entirely relieved of symptoms.

TABLE 3

Patients alive at the present time.....	33
1 patient is living 10 years after operation.	
1 patient is living 9.5 years after operation.	
1 patient is living 9 years after operation.	
1 patient is living 8 years after operation.	
2 patients are living 7.5 years after operation.	
1 patient is living 7 years after operation.	
1 patient is living 6 years after operation.	
2 patients are living 5 years after operation.	
1 patient is living 4.5 years after operation.	
3 patients are living 4 years after operation.	
2 patients are living 3.5 years after operation.	
4 patients are living 2.5 years after operation.	
3 patients are living 1.5 years after operation.	
10 patients were operated on during the past year.	

In our series of 35 cases in which operations were done there were 2 deaths. In each instance death occurred on the second day; both

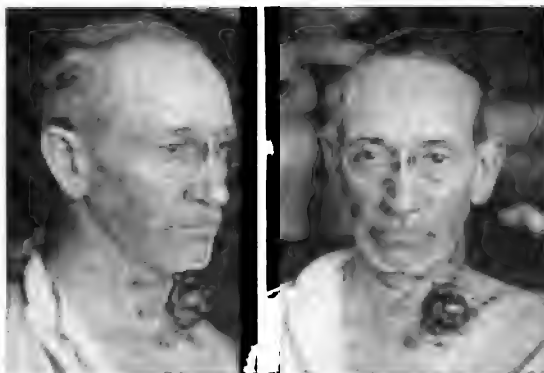


Fig. 15

Fig. 16

Figs. 15 and 16 (210857).—Photographs made about the eighth day after the first stage of the two-stage operation. The diverticulum is dissected from the tissues of the neck and the skin is sutured to the neck of the diverticulum. The second stage consists of the removal of the sac. No anesthetic is required in the second stage.

patients were very old and feeble. In one of these, because of many general contraindications to operation, we taught the patient to pass a stomach-tube, and for some months he lived by feeding himself in that manner; then the sac became so large that it produced a great deformity in the esophagus. The patient could no longer pass the tube and an

operation seemed imperative. The first stage of the operation was performed, but death took place suddenly the next morning. The history of the second patient is much the same, except that the sac was smaller and was removed at one operation. This patient also died the morning following the operation. In two of the remaining cases there was some evidence of a recurrence of the diverticulum. One of these patients was entirely relieved by passing a sound a few times, but in the other

case it was necessary to reoperate for the recurrence. We have recently corresponded with nearly all of the 33 patients and found them to be entirely free from symptoms.

I believe that the infolding operation and the two-stage operation are the procedures preferred and can be performed with practically no mortality.

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# SYPHILIS OF THE STOMACH: A REPORT OF FORTY CASES IN WHICH THERE WERE DEMONSTRABLE LESIONS AND THERAPEUTIC CURE OR IMPROVEMENT\*

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A renewed and growing scientific interest, a gradual increase in our knowledge, and a certain amount of controversy and skepticism, are centered about visceral syphilis, and particularly about one of its interesting forms, gastric syphilis. To the internist this phase of the condition should make a peculiar appeal because of the rarity, the difficulty of recognition and satisfactory diagnosis, the problems arising in differential diagnosis, and because the management of the disease lies almost entirely within the domain of medicine and is so frequently attended by brilliant therapeutic results.

No other problem in internal medicine, in my experience, seems to require more careful scrutiny and judgment, or closer consideration of all data. Enthusiasm, on the one hand, may influence one to accept or report that which has not been satisfactorily proved, while undue conservatism or a lack of clinical foresight may cause one to reject or overlook that which is, or eventually proves to be, a specific lesion. Certain inherent characteristics explain or give rise to clinical uncertainties, but these are readily outweighed by the fascination the observer experiences when in the actual presence of this most protean and ubiquitous of all human diseases.

I shall review briefly the essential pathologic anatomy. The gross gastric lesion is a tertiary, usually late, manifestation of the disease, both in the hereditary and in the acquired form. It is the result of a circumscribed or diffuse gummatous infiltration of variable extent, a chronic productive inflammatory process, usually having its origin in the submucosa. This process may involve any or all the structures of the organ, but having a predilection for the pars pylorica, it often ex-

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tends well upward along the lesser curvature, and to a lesser degree involves the greater curvature. Syphilitic ulcer, often multiple, is the expression of a broken-down gumma involving the mucosa and submucosa, or it may occasionally arise as the result of an obliterating endoarteritis. The sequelæ invariably are scar tissue from cicatrization with or without stenosis or hour-glass deformity, and fibrosis due to dense connective-tissue formation, resulting invariably in a deformed, contracted, thickened organ in advanced, untreated cases. Profuse hemorrhage, perforation, or fistulous formation is of rarer occurrence than in the benign ulcer cases, but a hyperplastic chronic perigastritis is relatively more common. Gummas, like benign ulcers, may heal spontaneously, leaving scars or deformity of variable degree. In addition to these gross changes there is considerable pathologic evidence to prove the existence of a syphilitic gastric catarrh, which may be a manifestation of the secondary or tertiary stage, the direct or indirect result of the infection. Thus, symptomatically and anatomically, specific gastric disease may simulate benign chronic catarrhal gastritis, ulcer and its sequelæ, fibromatosis, scirrhus carcinoma, and tuberculosis of the stomach, but from the therapeutic standpoint the difference is striking. To the experienced clinician, radiologist, and surgeon, there are certain extrinsic and intrinsic factors, not pathognomonic, but highly suggestive of specific disease. These differ from the usual characteristics of the other conditions noted, and have an invariable differential diagnostic value.

The proper interpretation of the sources underlying gastric disturbances in syphilitic suspects or in proved tertiary syphilitics may give rise to some difficulty, and in my study of a considerable amount of material, numerous questions have presented themselves.

A large majority of syphilitics make no complaint of gastric malfunction. Observations in this respect by various authorities show similar findings. McNeil, in a review of 1200 clinical syphilitics, states that only 97, or about 8 per cent, complained of some more or less serious forms of gastric disease, among which there were only 2 cases of organic syphilis. White reports that of a group of 600 syphilitics with strongly positive Wassermann reactions (excluding those with hepatic cirrhosis, lues hepatica, nephritis, and tabes), 44 (7.3 per cent) had prominent gastric symptoms. In 35 cases no definite lesion of the stomach was proved; in 9, actual luetic or coincident lesions were found (ulcer, gumma, or cancer). It is readily apparent that a variable com-

bination of factors in the group of syphilitics having gastric disturbances may give rise to considerable speculation and to diagnostic difficulties when taken in conjunction with the results of specific therapy. To avoid confusion and for practicable considerations the discussion in this paper will be confined to the demonstrable gastric lesions.

There are various factors that enter into the determination of the specific nature of a gastric lesion. By conforming to the requirements laid down by Chase, it would seem that many of the doubtful cases could be readily excluded. These requirements are: (1) Positive Wassermann reaction; (2) evidence of syphilis elsewhere in the body; (3) demonstration of a lesion in the stomach by the radiograph, and (4) therapeutic improvement.

#### POSITIVE WASSERMANN REACTION

Obviously, it will be seen that there may be instances of gastric syphilis without a consistent positive Wassermann reaction having been procured, at least not on the first attempt. It is a common experience to find, for example, definite evidence of cutaneous syphilis in which the reaction was not obtainable but in which there was a history of a primary lesion or exposure and therapeutic cure.

The provocative Wassermann test has helped us definitely in three of our cases. The test seems clinically inapplicable, however, owing to the amount of labor involved. After a study of 103 provocative tests, Stokes is of the opinion that it is of the least service of any of the diagnostic tests in active, deep-seated visceral, osseous, and central nervous system syphilis. The sensible conclusion is that clinical judgment and the therapeutic test are superior to this procedure in the diagnosis of obscure cases.

It is sometimes difficult to obtain additional evidence of syphilis, but by painstaking, systematized search, and by having in mind all the various manifestations of the disease, we frequently find evidence of the existence of syphilis elsewhere.

From my own experience, all gross syphilitic lesions could be easily demonstrated in the radiograph, and this is one of the requirements with which we are most readily able to conform. It is quite obvious, however, that small areas of gummatous involvement, or cases of single or multiple shallow ulcers, characteristic of the syphilitic type, and all cases of syphilitic gastritis especially, may easily escape detection.

## THERAPEUTIC IMPROVEMENT

Practically all syphilitics show prompt improvement clinically under adequate treatment whether or not they actually have a gastric lesion, but structural improvement in the stomach itself would argue strongly for the true specific nature of the trouble. Thus all the requirements may not be definitely fulfilled or the results may even go beyond the bounds of these requirements, and the condition still be essentially specific. In our later series (18 or 20 cases) these requirements were easily met.

Bearing in mind the foregoing, one has a fairly definite working criterion on which to prove or disprove the specificity of the lesion co-existing with syphilis. Benign or malignant gastric lesions may obtain as readily in the syphilitic as in any other type of individual and the proof or disproof of the syphilitic nature of the lesion under these circumstances would seem to depend largely on the degree of response to adequate antispecific treatment or, if possible, on the histologic examination of the tissue resected. There seems to be a lack of direct evidence to show that a syphilitic gastric lesion ever assumes a malignant form or that a benign ulcer becomes gummatous in the presence of systemic syphilis.

Among the questions that naturally arise are: What proportion of round ulcers, so called, classified as benign calloused ulcers, are actually syphilitic in origin? And what rôle may the symptomatology and the gastric chemistry in combination with results of serologic examination, play in their recognition? The same question may be raised with respect to duodenal lesions. In such cases Neumann has reported cases found at necropsy of duodenal ulceration, and yet the same author stated that probably 20 per cent of all round ulcers were syphilitic in origin, a statement with which we cannot agree. Mortimer has recently reported a fairly reliable instance of duodenal syphilis. Our experience prompts me to state that syphilis is a negligible factor in simple, uncomplicated gastric or duodenal ulcer, especially when associated with hyperacid gastric contents and the generally accepted syndrome of benign ulcer, with the possible exclusion of circumscribed syphilitic ulceration and stenosis of the pylorus. Simple ulcers associated with achylia or sub-acid values may have specific etiologic significance. It is to be remembered that the radiographic demonstration of a lesion is anatomic and not etiologic. The incidence or history of syphilitic disease or the finding of



positive Wassermann reactions or other evidences of syphilis in ulcer-bearing patients as we see them, is exceedingly rare, occurring in about one-third of 1 per cent. Such lesions undergoing intensive antispecific treatment are invariably uninfluenced, with a consequent indifferent influence on the gastric disturbance. In instances of gastric cancer the differentiation from syphilitic lesions is made with greater difficulty and uncertainty. In a careful perusal of the literature and with frequent misgivings in regard to our own cases, I have been impressed with the frequency with which ulcers have been excised or other surgical procedures carried out, or with which gastrectomies have been performed for supposed cancer when the specific nature of the lesion was probably never discovered or thought of as a possibility.

Pathologists still consider syphilis of the stomach as more or less of a curiosity. In a review of the literature I found that only about a dozen of the cases clinically diagnosed syphilis of the stomach have been verified by histologic examination. The meager results in necropsies performed on subjects with late acquired or congenital syphilis, for example, those by Chiari, Stolper, and others, and more recently by Symmers in this country, seem to warrant their conclusions. Symmers, after finding only one ulcer of indubitably syphilitic origin in 314 necropsies, states that unless the diagnosis of gastric syphilis is confirmed by microscopic examination he is not inclined to accept it. For scientific reasons it is to be regretted that all fairly authentic cases of gastric syphilis do not come to necropsy, but fortunately when such cases are recognized the condition responds so favorably to treatment that post-mortem evidence is not available. The number of reported cases which have been diagnosed clinically is approximately 200. It would seem that a considerable number of the earlier cases and some of the recent ones cannot, in the light of our present knowledge, be accepted as definite instances of organic gastric syphilis because they have been incompletely studied.

The era of serology and radiology has naturally given an impetus to renewed interest in and to more reliable insight into these obscure conditions, and has made numerous reliable case reports possible. Serology and radiology are useful diagnostic agents which have furnished data necessary to conclusive clinical diagnosis, the disquieting attitude of the pathologist notwithstanding. After all, the discrepancies between the attitude of the pathologist and that of the clinician may be more apparent than real. If the case reports not adequately proved

are excluded, and if we recall the universal distribution of syphilis and its incidence,—from 10 to 15 per cent alone of the urban population of Europe are infected,—it will be seen that the number of case reports is not large even though the incidence of organic gastric disease in such cases is remarkably small. In view of this I do not feel that we have any apology to offer for having thus far recorded only 40 authentic instances of the disease during an investigation of more than 6000 proved cases of ulcer and cancer of the stomach, and exclusive of several thousand other cases in which the clinical diagnosis of a gastric lesion was established beyond cavil. In all probability numerous other instances of luetic involvement have been overlooked.

While it is apparent that ultimate diagnosis depends on the demonstration of spirochetes microscopically in the exsected tissue, yet the grouping with all the evidence from all sources may maintain a diagnosis as conclusively as many others which are freely accepted. After all, there is no decisive ultimate diagnosis, particularly in the cases of acquired syphilis, because up to the present time spirochetes have not been demonstrated in the gastric tissue and we know that the histopathologic criteria are not conclusive.

Without going into statistical details, which are always tiresome and easily forgotten, I will simply call attention to the more tangible data and deductions arrived at in a study of 40 cases in 12 of which the patients came to operation. There were 29 males whose average age was thirty-seven years; and 11 females of thirty-five years' average age. Total average, thirty-six years. All the women were married, and 3 admitted they were or had been prostitutes. The primary lesion was a genital chancre in all the cases that could be determined, except in four instances; 2 of these infections occurred in surgeons and represented an innocent infection of the finger; 2 others were cases of heredosyphilis. Wassermann tests were made in 35 cases; the remaining 5 cases antedated the routine use of the test, but were verified by surgical exploration and postoperative therapeutic management. Thirty-one of these 35 cases gave strong reactions. Four reacted later or the reaction was obtained by the provocative method, and in one the reaction never became positive. Six of the 31 patients with initial positive Wassermann reactions denied any luetic infection. The average duration of symptoms was a little more than two years. The earliest period of onset of symptoms after infection was one year, the latest twenty-eight years. The average period was twelve years. In syphilitic aortitis the average

period of the onset of symptoms after infection is about eighteen years. Thus it appears that the age incidence is of the greatest significance, averaging quite regularly thirty-six years, in contrast with the age incidence in ulcer, which is about forty-five years, and in cancer, which is fifty-four years. This average seems quite out of proportion to the extent of the pathology invariably present. Finally, symptoms develop on an average of twelve years after infection, which makes the average age of the patient about twenty-three or twenty-four at the time of the infection. These figures seem in keeping with the general age incidence in syphilis.

In the physical examination in the obstructing hour-glass cases, the patients were generally undernourished and about half of them were anemic but not cachectic. The objective evidence of syphilis elsewhere was routinely sought for and positive findings were made in proportion to the acumen of the general diagnostician.

In a series of 23 cases which I<sup>4</sup> reported several years ago I had noted the association of aortitis, aortic endocarditis, aneurysm, gummas of the liver or syphilitic cirrhosis, involvement of the spleen, cutaneous lesions, gummatous meningitis, etc., in about one-third of these cases. In the last 17 cases of the present series (40 cases) observed, more careful scrutiny showed greater incidence of other signs of syphilis, singly or in combination. They were recorded as follows:

Enlargement of the lymphatic glands, usually general in distribution, especially those involving the postcervical and epitrochlear nodes, occurred in 10 cases. In one case an abdominal mass, regarded as gummas or hyperplasia of the mesenteric lymphatics, was discovered as this enlargement disappeared under treatment. Next in order were evidences of involvement of the central nervous system. Irregular or unequal pupils were recorded in 6 cases, disturbances of the pupillary reflexes in 2, frank tabes in one, internal ear deafness in 2, and disturbances of the superficial reflexes in 2. In the cutaneous system a papillary eruption was recorded in one case, healed lesions or scars in 3, genital scars in 4, a venereal wart of the prepuce in one. Defect, perforation, and crusting were noted in the nasopharynx in 4 cases and saddle-nose in one. Tibial periostitis was recorded in one case, splenic or liver involvement in 4 cases. The cardiovascular system objectively was intact in all of these cases.

### SYMPTOMATOLOGY

In a careful and detailed review of the case histories the classification would seem to depend most logically on the extent and site of involvement, and we have therefore naturally grouped them under such classification in three groups:

1. Cases in which there are circumscribed pyloric lesions associated with normal or subacid values, with or without stenosis.
2. Cases in which there are fairly circumscribed lesions irrespective of the site, associated with achylia.
3. Extensive lesions with hour-glass deformity or general marked contracture or cirrhotic stomach, usually associated with achylia.

The cases in the first group simulate closely benign lesions at the pylorus. Owing to the intermittent course of the disease at the outset the characteristics, delayed pain and distress following alimentation, are controlled wholly or in part by alkalis, foods, liquids, posture, etc., and differ from benign lesions in that the course is more rapidly progressive. The relief afforded by food, alkalis, etc., soon disappears. The onset of pain is quite promptly after meals in the later course, and the symptoms then do not respond to treatment by ordinary methods of diet and medication.

In the cases in the second group, characterized by lesions not extensive and by associated achylia, the symptoms are not exactly like those of either ulcer or carcinoma. The onset of pain is usually promptly after meals, and the other associated symptoms simulate those of chronic catarrhal gastritis.

In the third group of cases in which there is extensive involvement or hour-glass deformity or both, the symptoms are variable. They are usually the result of mechanical factors; that is, the introduction of food promptly occasions distress, owing to a markedly reduced capacity. The condition is characterized by a feeling of fullness, sometimes a bursting sensation, and such patients immediately attempt to vomit in order to relieve themselves. Anything which removes the gastric contents affords relief. The high hour-glass stomach may merely regurgitate, as in patients with obstructions high in the pars cardiaca or in the lower esophagus. In two such cases the patients did not complain of any pain—they merely regurgitated. Still other disease conditions simulate the clinical picture of this group, for example, scirrhus carcinoma of the stomach, dyspepsia associated with gallbladder disease, or gastric disturbances associated with certain fevers. Radiographic

evidence of marked gastric pathology present in an adult, between the third and fourth decades of life, and the absence of cachexia, strongly suggest the possibility of syphilis.

Pain was present in 39 of the 40 cases and was characterized as severe in 10. The favorite method of relief was by vomiting in 32 cases (82.5 per cent). Pain appeared immediately or fairly promptly after eating in 26 cases (65 per cent); it was constant in 8 (20 per cent); at some variable time after meals in 5 (12.5 per cent). While nocturnal pain is commonly regarded as a frequent characteristic of syphilitic lesions, benign gastric lesions with supersecretion or stasis will frequently have this characteristic; but in gastric lesions associated with achylia the nocturnal pain may point to a luetic origin. However, this is not a feature on which we place much diagnostic significance. Hemorrhage is comparatively rare, being recorded in only two instances (5 per cent); emesis, nausea, and flatulency were the chief symptoms, next to pain. Quite contrary to all malignant lesions of the stomach which gastric syphilis simulates in chemical and radiologic characteristics, the appetite was noted as about normal in 49 per cent and ravenous in 7.5 per cent of the cases. In other words, more than 55 per cent of the patients had normal or increased appetite. Complete absence of appetite was recorded in 12.5 per cent. The average loss of weight was 35 pounds; 50 per cent had lost from 40 to 75 pounds. Patients with multiple hour-glass stomach or marked cirrhosis, especially the hereditary type, showed an extreme grade of malnutrition.

In the examination of the gastric contents the number of patients without free acid or ferments was 32 (80 per cent). Those with free hydrochloric acid were 18 (20 per cent). The number with achylia alternating with free hydrochloric acid was 3 (7.5 per cent). In one there was a return of free hydrochloric acid after intensive treatment. Thus unquestionably, with the exception of cases of obstructing circumscribed lesions at the pylorus, practically all cases of gastric syphilis are associated with achylia or rarely with subacid values. This is an important fact always to be borne in mind and it is verified by authentic recent case reports as well as by observers who have carefully searched the literature for reports of authentic cases in which the gastric chemism was given particular attention. The absence of free acid in these non-obstructed cases is partly due to mechanical factors and to the influence, local as well as systemic, of the infection on the gastric mucous membrane. In those cases of actual specific gastric lesions, indirect in-

fluences involving the pancreas, the liver, and the system generally also play a part.

### PATHOLOGY

In view of the short duration of the disease, averaging a trifle more than two years, the changes that take place in the stomach are extensive. Such changes seem to be dependent more directly on the duration



Fig. 17 (175711).—Syphilitic hour-glass with obstruction. Female, aged thirty-eight; probably heredo-syphilis. Gastric symptoms fourteen months, pain and emesis, achylia. Wassermann + + + +. Marked improvement after prolonged course of treatment. Gain, 40 pounds. Recovery not complete, probably because of the obstruction present. No re-ray. Operation may be necessary. The illustration shows a markedly dilated esophagus; this type is most characteristic of the radiographic appearance of gastric syphilis.

of the infection than on the duration of the symptoms of gastric malfunction. Cases in the exudative stage may show extensive infiltration that will clear up completely under treatment if the condition is recognized and treatment instituted in time. Much may be conjectured as to the pathogenesis of the condition in view of the disproportion between the duration of the clinical symptoms and the pathology. Twelve of

concerned the lower third of the stomach; next in order the media, including those cases of hour-glass which are usually found in the upper or middle third, and, finally, the general marked involvement of the



Fig. 20 (145508).—Extensive syphilitic cirrhosis and contractures involving chiefly the middle and lower third. Heredосyphilis. Male, aged twenty-five. Wassermann negative. Gastric disturbances seven years. Discomfort after eating small amounts of solid foods. Regurgitation. Exploratory operation three years previously. Numerous stigmas; moderate symptomatic improvement following antisyphilitic treatment.

cirrhosis cases; the rarest form is that in which the pars cardiaca alone is involved.

Carman, in a survey of the material herein reported, deduces the following as quite characteristic of gastric syphilis:

1. Filling defect of the gastric outline, usually without corresponding palpable mass.
2. Shrinkage of gastric capacity.
3. Stiffening and lessened pliability of the gastric wall.



Fig. 21 (208425).—Syphilis of the pars cardiaca, rare form, easily mistaken for carcinoma. Patient male, aged thirty-three. Primary lesions twelve years previously, gastric disturbances one and one-half years. Distress in epigastrium after food. Six months ago onset of emesis after all food except milk and small amounts of milk toast. Wassermann +++ (9/20/17). Radiologic diagnosis: inoperable carcinoma of the stomach. Filling defect cardia. Intensive course of treatment here with marked improvement. Gained 17 pounds. Ravenous appetite. Wassermann negative 10/20/17. Radiograph 11/5/17. Condition shows marked anatomic improvement. To date patient is clinically cured.

4. Absence of peristalsis from the involved area.
5. Pylorus gaping rather than obstructed.
6. Six-hour retention less common than in other gastric lesions (23 per cent).



7. So-called hour-glass stomach; upper loculus expanded and bulbous, lower loculus tubular, due to extensive irregular concentric contraction.

8. Patient usually under cancer age and not ill in proportion to the extent of disease shown by the x-ray.

One can see the significance of such radiologic data in combination with the results of serologic examination or other clinical evidence of syphilis, irrespective of the clinical syndrome which seems still generally unrecognized, or not entirely clarified, but which will prove to be a fairly applicable working factor in the diagnosis.

The antisyphilitic management of all these cases was fairly intensive, depending somewhat on the degree of response to the Wassermann test. In the initial treatment the patients received at least six intravenous injections of salvarsan, neosalvarsan, or arsenobenzol at intervals of a week. During and subsequent to this period from 21 to 36 injections of a soluble salt of mercury were given intramuscularly or a course of vigorous mercurial inunctions was applied. A repetition of this treatment was carried out either at the clinic or under direction of the local physician. The end results are encouraging. Of the series of 40 patients, 38 were heard from. Those clinically cured were 16 (42 per cent). Those regarding themselves as improved were 19 (50 per cent), or a total of 92 per cent. Three stated that they were not improved, representing a failure of 8 per cent. Twenty-two of the patients were reexamined, including a re-ray, and of these 8 (36.6 per cent) were anatomically improved. Several underwent a total anatomic cure. We feel that this percentage could be increased considerably if all the patients had been reexamined, but many of them live at a considerable distance, and, being clinically improved, have had no incentive to return for further treatment or study.

It is obvious that all dyspeptics with a definite history of primary or secondary lesions, or a suspicious genital sore of any description, or repeated gonorrheal infection, would rouse the suspicion that the disturbance might have its origin in syphilis. This is true in married persons whose union is childless or marked by spontaneous abortions, miscarriages, or premature or still births; in patients, usually young adults, exhibiting signs of heredosyphilis; in all cases of gastric malfunction in which there are objective signs of syphilis in the absence of an infection; in all atypical gastric disturbances; and in all cases in which response to the usual dietetic and medical management is inadequate. In developing

a history of syphilitic infection, the greatest difficulty is encountered in the female patients, the majority of whom often remain in ignorance of the exposure or the nature of the infection when present. A composite clinical picture may be constructed as follows:

The patient is an adult, averaging thirty-five years of age. Usually the gastric disturbance averages a little more than two years' duration, characterized chiefly by pain, vomiting, and flatulency coming on fairly promptly, after taking food. The course is progressive, with gastric chemism and x-ray findings—more like that of carcinoma. The patient is undernourished but not cachectic, may be somewhat anemic, and there is usually absence of any palpable gastric mass. The gastric lesion is invariably extensive, is occasionally localized in the pyloric area, with only a slight tendency to produce stenosis. Such characteristics, in conjunction with a positive Wassermann reaction or with a history of infection and other clinical signs of syphilis, are strong presumptive evidences of specific gastric disease.

Bearing these characteristics in mind and that which further proves their reliability, the disclosures of the fluoroscope and radiogram in combination with the results of gastric analysis or the demonstration by the surgeon of a fairly extensive ulcerating mass in a more or less generally involved stomach, especially in an adult between the third and fourth decades, has in numerous instances uncovered a specific history previously concealed, or has pointed out the necessity for serologic examination. In other words, the diagnosis of systemic and visceral syphilis has been worked out backward, insofar as gastric syphilis is concerned, by the employment of reliable proved diagnostic data.

#### SUMMARY

1. Organic gastric syphilis is rare even in advanced cases. The average age incidence was between thirty-five and forty years, the average duration of the symptoms about two years, and the average duration of the infection about twelve years.

2. Exclusive of the congenital cases and the advanced obstructing hour-glass types, cachexia was rare, anemia was not marked, and there was an invariable absence of gastric tumor.

3. The syndrome was not characteristic but was usually variable, depending largely on the site and extent of the involvement. The localized gummas of the pylorus, with or without stenosis and with free hydrochloric acid in the gastric extract, simulate benign pyloric ulcer;

in obstructing high hour-glass, the patients usually have considerable pain and vomiting soon after taking food; in the contracted and deformed types there are distress, pain, and associated symptoms in proportion to the nature and amount of the food taken. The symptoms in the main closely approach those characteristic of a slowly progressive form of scirrhus carcinoma. The symptoms common to all the cases were: A fairly marked progressive course, prominence of pain soon after eating, invariably associated with nausea and vomiting, the absence of hemorrhage, maintenance of appetite in the majority of cases, and marked loss of weight without definite cachexia.

4. Achylia was present in over 80 per cent of the cases; in 20 per cent there was free hydrochloric acid in the gastric extract but usually with subnormal values. In 7.5 per cent of the latter achylia alternated with free hydrochloric acid secretion.

5. The pathologic anatomic process was a gummatous infiltration, diffuse or circumscribed. Syphilitic ulceration of the mucous membrane was generally a secondary phenomenon. There was a predilection for the pylorus and media and extension upward along the lesser curvature. Hour-glass contractures as a rule involved the pars media. Pyloric stenosis is more infrequent than in benign ulcer and malignant conditions, approximately 20 per cent. Gastric involvement was usually extensive even when the symptoms were of brief duration. General diffuse syphilitic cirrhosis was characteristic of the congenital cases. In advanced cases hour-glass contracture, marked thickening, deformity and contracture due to fibrosis were the rule.

6. Intensive antisiphilitic treatment in the early stages may produce actual clinical and anatomic cure. In advanced cases there may be little or no response. This series showed clinical cure in 42 per cent and improvement in 50 per cent, representing a total of 92 per cent improved or cured. (This includes 12 patients, 30 per cent of the cases, who required surgical interference.) Treatment had no influence in 8 per cent. Of the patients reexamined, 36.6 per cent showed anatomic improvement, 3 having complete anatomic cure.

7. The proof of the specificity of a lesion involves numerous factors. Differential diagnosis is often exceedingly difficult. The requisites are: Demonstrable evidence of a gastric lesion, positive Wassermann reaction or other reliable evidence of syphilis elsewhere in the body, or both, and definite, sustained therapeutic improvement. These factors in conjunction with achylia or subacidity in the majority of cases, with the

radiologic characteristics herein described, in addition to anatomic improvement or cure, seem to make the clinical or intra vitam diagnosis of syphilis of the stomach conclusive.

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There are occasional striking exceptions: An ulcer on the greater curvature may be accompanied by an indrawing of the lesser curvature; an ulcer in any situation may contract the walls of the stomach in the plane of its site; the isthmus, instead of being short, may be relatively long. The width of the canal is, of course, variable, but even when it is quite narrow, the constriction is nearly always sufficiently emphatic to be readily noted.

Gastric syphilis, which is more often recognized now than in the past, probably ranks second to simple ulcer in producing hour-glass stomach.

Gastric cancer, as a causative factor in hour-glass stomach, probably ranks next in importance; but this has been found to be an accompaniment in less than 1 per cent of the cases. The cancer may be of the



Fig. 22 (192198).—Organic hour-glass stomach in a case of gastric tuberculosis. Postmortem confirmation.



Fig. 23 (191830).—Spasmodic hour-glass stomach after gastrostomy, done eighteen years ago in a case of cardiospasm.

annular type, encircling and constricting the gastric circumference, or, if localized at either curvature at the anterior or posterior wall, it may produce contraction of that segment of the stomach. Again, a cancer mass projecting into the lumen of the stomach may divide it into two chambers. Sarcomas or benign growths may cause a similar biloculation, but such tumors are not of common occurrence.

A hyperplastic form of tuberculosis is occasionally met with in the stomach, the process involving the pyloric end of the stomach without hour-glass deformity. However, tuberculous ulcers, which are often multiple and seated in the midstomach, may constrict this portion (Fig. 22).

More or less contraction may ensue following certain operations,

notably gastrostomy, gastro-enterostomy, sleeve resection or local excision of gastric lesions (Fig. 23). After gastrostomy or sleeve resection the contraction may be fairly pronounced, but after gastro-enterostomy there is usually no constriction unless a gastrojejunal ulcer develops or extensive adhesions form (Figs. 24 and 25).

Hour-glass contraction has resulted from scarring due to corrosive chemicals, such as muriatic acid, as in a case reported by Klein.

Perigastric inflammatory processes of various kinds may produce bands or adhesions and cause hour-glass deformity. Occasionally cases of hour-glass are found to be caused by a single adhesion band of unknown origin (Fig 26). In Elder's case the stomach was drawn up by a ligamentous band from the right rectus muscle. Mayo Robson men-



Fig. 24 (94543).—Spasmotic hour-glass constriction following sleeve-resection for multiple gastric ulcers. Contracture at point of anastomosis.



Fig. 25 (191809).—Spasmotic hour-glass constriction following sleeve-resection. The narrowing is at the point of anastomosis.

tions an instance in which the stomach was trilocular, one constriction (the proximal) being caused by a band of adhesions from the liver to the transverse colon, while the other stenosis was due to the cicatrization of a chronic ulcer.

Conflicting statements have been made as to the relative size of the two pockets in organic hour-glass, particularly the common form due to ulcer. Tuffier and Roux-Berger generally found the narrowing to be nearer the pylorus than the cardia; hence the upper pouch was the larger. On the other hand, Eusterman found the lower loculus to be the larger in a considerable number of cases. X-ray examination of the cases in the Mayo Clinic for five years past would indicate that in the majority of instances the upper pocket was the larger, but this dis-

cordance in observations is rather immaterial. Moynihan has found that the proximal portion has thicker walls than the pyloric portion and is larger by reason of dilatation and hypertrophy.

Among the complications of organic hour-glass, volvulus has been observed by Hermes and Reinecke. In Hermes' case the hour-glass constriction was the size of a finger. The pyloric loculus had rotated on its long axis, protruding through a slit in the mesocolon. In Reinecke's case, also, there was a volvulus of the pyloric segment, causing complete stenosis at the hour-glass constriction.

Referring to *spasmodic* hour-glass stomach, the rôle played by spasm in the production of this condition has become better understood with the increasing employment of the radiologic examination. Surgeons have sometimes noted peculiar spastic manifestations in the stomach



Fig. 26 (212801).—Hour-glass stomach due to adhesions, in a case of cholelithiasis and chronic appendicitis. Stomach and duodenum negative. Radiogram made after deep inspiration.



Fig. 27 (179078).—Intrinsic hour-glass stomach. Case of gastric ulcer without crater formation. Contracture appears much deeper in radiogram than it did at operation.

during operation. For example, W. J. Mayo, while operating, has on several occasions seen such spasms in which the stomach slowly contracted, the gastric wall became thick and blanched, and then as slowly relaxed again. But the significance of this spasm was not appreciated until the radiograph and the opaque meal came into common use. One of the earliest discoveries was the fact that the barium-filled stomach sometimes showed a spasm of the circular muscle-fibers in the plane of a gastric ulcer, thus producing an indentation on the opposite curvature, the incisura. Later, more diffuse forms of spasm were recognized and the whole subject of gastrosplasm became an important chapter in gastric radiology.

The particular forms of spasm producing hour-glass stomach may be classified as *intrinsic* and *extrinsic*.

Intrinsic spasm is a convenient designation for spastic contraction of the gastric musculature arising directly from a lesion of the stomach itself. In the majority of cases the lesion is an ulcer, and most often the circular fibers chiefly are affected (Fig. 27). When the stomach is filled with barium, the spasm is radiologically observed opposite the ulcer as a local indrawing of the curvature, commonly the greater. It is in this form that the indentation may be relatively slight in some cases or so deep in others as almost to bisect the stomach. Cancer may also produce a similar local spastic indrawing of the gastric wall (Fig. 28), and spasm is probably accountable in some cases for the hour-glass contraction accompanying tuberculous and syphilitic lesions.

The view has been expressed by Moynihan and by Reizenstein and Frei that in many cases of organic hour-glass stomach the narrowing is exaggerated by spasm. This is unquestionably true.

Extrinsic spasm is either produced by lesions outside the stomach or is at all events accompanied by such lesions. It is an occasional cause of hour-glass deformity, as seen radiologically, and has been frequently noted in association with duodenal ulcer, disease of the gall-bladder or appendix, and sometimes in hysterical or other nervous states.

The purely spastic hour-glass deformity, whether of intrinsic or extrinsic origin, is rarely present at operation because of the relaxation produced by the anesthesia, and for this reason the radiologist is sometimes wrongfully accused of a maldiagnosis.

As to symptoms and signs, the clinical literature of hour-glass stomach is most exclusively devoted to the organic form. Agreement is general that the symptoms alone are not diagnostic. They may point rather definitely to ulcer, the most common causative lesion, but seldom suggest the complicating factor. In a few of the cases reported as congenital it is noteworthy that the patients, though adults, gave only a recent history of gastric disturbance.

On the other hand, the physical signs of the condition have been given considerable stress. Moynihan holds that these signs, in conjunction with the symptoms, enable a positive diagnosis to be made in the great majority of cases. Mayo Robson says: "While in nearly all cases the cause has been capable of diagnosis, the effect has also been diagnosed in some, and may be in nearly all cases if care and time be given the diagnosis."



Tuffier states that the importance of the clinical signs has diminished with the use of the radiograph. However, he sounds a warning to the effect that in spite of its precision a radiologic examination for hour-glass stomach may lead to error.

Moynihan's compilation of the physical signs, as quoted by Osler, includes the following:

1. A measured quantity of water is put into the stomach through the tube. The water is immediately withdrawn, but a portion fails to return, having been lost as through a hole (Woelfler's first sign).

2. The stomach is washed out until the fluid returns clear. There may then be a sudden rush of foul-smelling liquid regurgitated from the lower pouch (Woelfler's second sign).

3. The stomach is filled with fluid, and succussion sounds are elicited. After withdrawing the fluid as completely as possible, succussion sounds may still be noted because of liquid still remaining in the lower loculus (Jaworski's paradoxical dilatation).

4. Von Eiselsberg observed in one of his cases that on distending the stomach a bulging of the left side of the epigastrium was produced; after a few moments this gradually subsided and at the same time there was a gradual filling up and bulging of the right side.

5. Von Eiselsberg has also noted a hissing sound in the region of the constriction, while distending it with  $\text{CO}_2$  by administering separately the two component parts of a seidlitz powder. The noise is heard by applying a stethoscope two or three inches to the left of the midline.

6. By using a seidlitz powder in the same way, Moynihan has noted after twenty or thirty seconds an enormous increase in resonance of the upper stomach. Later, the pyloric pouch may fill and become prominent.

7. Schmidt-Monard, Eichhorst, and Moynihan have all seen cases which showed a distinct sulcus between the two pouches after distention with  $\text{CO}_2$ .

8. By filling the stomach with water and employing gastrodiaphany, Ewald has observed that the transillumination is seen only in the cardiac pouch lying to the left of the midline, while the pyloric pouch remains dark. He has also used the deglutable rubber bag of Hemmeter and Turck in a similar way: distending the bag causes a bulging of the cardiac pouch only.

While some of these signs carry more or less conviction, there are some which seem almost trivial. Notwithstanding the opinion of Mayo Robson and Moynihan that a positive diagnosis is possible in most

cases, it is noteworthy that neither they nor others report many cases as having been diagnosed clinically before operation, while it is obvious that the x-ray affords a practical and efficient means of diagnosis.

### X-RAY DIAGNOSIS

Since the essential feature of an hour-glass stomach is its biloculation by an intermediate constriction, it would seem that the choice of radiologic methods to demonstrate this fact is not important. It is conceivable that the x-ray examination might show the biloculation after air inflation more or less positively. However, by filling the stomach with an opaque meal, the deformity of the gastric outline is shown more definitely, and this method is almost universal (Fig. 29).



Fig. 28 (142921).—Intrinsic spasmodic hour-glass stomach in a case of colloid carcinoma on posterior stomach wall. The deformity was not affected by belladonna, and it was not found present at the time of operation.



Fig. 29 (143766).—Perforating gastric ulcer producing organic hour-glass stomach.

The screen examination is made with the patient standing and, if necessary, in the recumbent position also. Plates may be made with the patient in either position, but in hour-glass stomach the vertical is preferable.

Hour-glass deformity is so striking in the radiograph shadow of the barium-filled stomach that, save in exceptional instances, it can readily be recognized even by the novice. But, as Groedel well says, the diagnostic task has only begun with the establishment of the presence of an hour-glass form, for the radiologist should endeavor to distinguish between the following varieties: (1) Organic; (2) spasmodic, from an intrinsic lesion; (3) spasmodic, from lesions or conditions outside the stomach; (4) pseudo hour-glass.

In conformity with its pathologic anatomy the organic hour-glass resulting from gastric ulcer usually shows a B-form (Fig. 30) in the X-ray image, the constriction being at the expense of the greater curvature, which is drawn toward the lesser. Almost invariably the cleft is deep and relatively narrow, so that the loculi communicate by a short canal of small caliber. Indeed, the canal may be so stenotic that a portion of the six-hour meal is retained in the upper loculus, but this is exceptional. However, with a very narrow channel the stenosis may be evident by retarded passage of the barium water or barium pap during the screen examination, even if there is no retention from the six-hour meal, and in many cases it trickles very slowly through the aperture, running in a curvilinear course along the lesser curvature.



Fig. 30 (157751).—Organic hour-glass stomach in a case of gastric ulcer. The deformity gives the stomach the form of a capital letter B.



Fig. 31 (23008).—Organic hour-glass stomach in a case of perforating ulcer of the stomach.

With these conditions present, the observer can feel considerable certainty that the hour-glass is really organic. Cerné and Delaforge have called attention to another item of some diagnostic significance: the sagging of the upper loculus (Fig. 31). They describe the lower border as curved and encroaching upon the cleft, or else completely overhanging it, so that palpatory pressure may be necessary to demonstrate the constriction between the loculi. Often a niche, or accessory pocket, is seen on the lesser curvature side of the isthmus associated with hour-glass, and this favors the probability that the hour-glass is organic, although it is not conclusive proof. Fixation of the stomach, as evidenced by its resistance to efforts at palpatory shifting, also suggests that the deformity is organic. An important feature is the fact

that neither the position nor the contour of the constriction can be altered by manipulatory massage.

Carcinomatous organic hour-glass is easily recognized, as a rule. The isthmus may be centrally placed, often with a funnel-like expansion at either end, so that it has the form of a script *x* (Fig. 32). The contour of the canal is usually irregular, due to small projections from the tumor mass, and the dim shadows of the growth itself may be visible. If, in addition, a tumor corresponding to the filling defect can be felt, the evidence is reasonably complete. However, all the cases do not possess these typical characteristics; the growth may involve only one curvature, and in such instances the channel between the loculi lies along the opposite curvature. In many of the cases the condition is, strictly



Fig. 32 (172006).—Concentric ( ) type of hour-glass stomach in a case of gastric cancer.



Fig. 33 (173711).—High organic hour-glass stomach in a case of gastric syphilis. The Wassermann test was positive.

speaking, an hour-glass form of the gastric lumen rather than of the stomach as a whole, the local narrowing of the cavity being caused by the projection of the tumor into the lumen, and judging by the external contour of the stomach, as seen at operation, the surgeon would hardly consider it a true hour-glass. Medullary cancer especially may produce an hour-glass of this sort.

The scirrhus type, infiltrating the gastric wall, is more likely to result in actual contraction. It is interesting to note that the carcinomatous hour-glass seldom causes a six-hour retention in the upper loculus, even though the isthmus is quite narrow.

Syphilitic hour-glass may result either from luetic ulceration or hyperplasia. The hyperplastic or gummatous type with filling defects

and a corresponding palpable mass is not radiologically distinguishable from cancer. Syphilitic ulcers are often multiple, and their strong tendency to the production of hour-glass has been frequently noted (Fig. 33). Dewis believes that he has noted a characteristic point which differentiates it from cancer and simple ulcer: "In syphilitic hour-glass of the stomach we see a long, regular isthmus, at each end of which the walls of the stomach rise more or less abruptly or dumb-bell-like. This is in contrast to the sharp incision of simple ulcer hour-glass with practically no isthmus, and the picture differs quite as much from the cancer

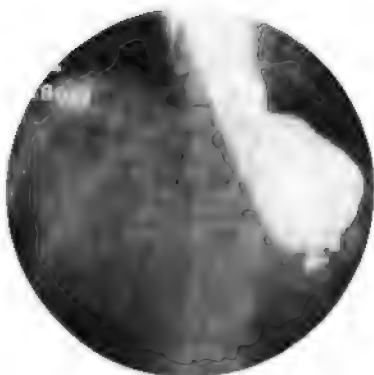


Fig. 34 (218041).—High hour-glass stomach with dilatation of the esophagus in a case of gastric lues. Wassermann positive.

In spite of sounding (25F) and antiluetic treatment the constriction became more marked. The patient lost weight rapidly, from 118 to 79 pounds. Fluids were taken with great difficulty and operation was thought advisable.

Findings at operation: Stomach about 10 centimeters long and from 6 to 7 centimeters in diameter. For a distance of 4 centimeters extending from the pylorus up to the constriction the stomach was contracted to about 1 centimeter in diameter.

Operation: Sleeve-resection, with removal of two-thirds of the stomach. Jejunostomy.

hour-glass with the infiltrated walls of the stomach sloping irregularly away from the constricted portion" (Fig. 34). This dumb-bell appearance has also been described by LeWald. We have occasionally observed the appearance which Dewis and LeWald describe, and sometimes fancied that the shadow of the barium-filled luetic stomach showed a peculiar "flatness" as compared with the radiograms of other lesions. As a matter of fact, however, the radiologist's first suspicion that the lesion is syphilis rather than cancer is usually aroused not by the *x-ray* picture so much as by certain obvious clinical facts. There is the absence of a palpable mass, the patient may be under the cancer age, he is anemic rather than cachectic, and has not lost weight and strength

in proportion to the extent of gastric involvement and the duration of his trouble. Then, with a positive Wassermann, the diagnosis of lues is warranted, but hardly otherwise.

All forms of organic hour-glass stomach have certain features in common: they are persistent at successive examinations, constant in situation, cannot be effaced by epigastric massage, and remain unaltered after the patient has been given atropin or belladonna to physiologic effect.

Purely spastic forms of hour-glass, produced directly by gastric

lesions and hence conveniently designated as "intrinsic," are seen in association with ulcer and cancer. As stated before, the spastic hour-glass of ulcer, like the organic form, is seen opposite the ulcer in the shape of an indentation of the curvature, usually the greater (Fig. 35). The depth of the indentation varies, but is nearly always greater than its width. Occasionally, when the indrawing is not very pronounced, it may appear as a triangular notch. Each of two or more ulcers may produce an incisura either separately or, if the ulcers are closely adjacent, fused irregularly together so that the margins are not clean-cut. As a rule, the single, deep, spastic incisura is regular in outline, with straight, parallel sides, and this appearance is of some value in distinguishing it from an organic constriction. However, such characteristics have also



Fig. 35 (146382).—Perforating gastric ulcer. Spasmodic hour-glass stomach. Not affected by belladonna because intrinsic in cause and not present at operation because relaxed by the narcosis.



Fig. 36 (140035).—Intrinsic spasmodic hour-glass stomach. Malignant ulcer of the posterior wall of the stomach.

been observed in organic hour-glass stomach (Figs. 29 and 30). In other respects it does not differ from the organic variety, is constant in situation, present at a second examination, cannot be obliterated by palpatory maneuvers, and is still present after the administration of anti-spasmodics.

Spastic contraction is associated with gastric cancer less frequently than with gastric ulcer. Usually it is seen as an indrawing of the greater curvature opposite the growth and is considerably wider than the contraction produced by an ulcer. Holzkecht has spoken of it as the "broad incisura" of cancer (Fig. 36). The luminal margin of the contraction is often irregular. Rarely a small cancer may provoke a narrow spastic contraction, resembling that of ulcer. The broad spasmodic

contraction may be mistaken for a filling defect produced by the growth itself, but close inspection of the plate will show that the indentation is clearly outlined without any faint shadow of a tumor mass between the borders, although a shaded filling defect corresponding to a palpable mass may be seen directly opposite the contraction. The whole picture is, as a rule, so plainly indicative of cancer that the examiner will have little interest in the question whether the hour-glass is organic or spasmodic, or both. That spasm probably accentuates the various forms of organic hour-glass deformity is supported by the fact that the isthmus depicted by the radiogram is often much narrower than when exposed to view at operation.

Spasmodic hour-glass contraction resulting from, or at all events associated with, conditions outside the stomach is one of the most de-



Fig. 37 (20594).—Extrinsic spasmodic hour-glass stomach which relaxed after belladonna to physiologic effect. Note Fig. 38.



Fig. 38 (20594).—Same case as Fig. 37. Stomach normal in outline after giving belladonna to the physiologic effect.

ceptive manifestations with which the radiologist has to deal (Fig. 37). Although a definite etiologic relationship is difficult to establish, there are three conditions which are especially prone to be accompanied by some form of gastrospeasm, namely, chronic cholecystitis, chronic appendicitis, and duodenal ulcer. Gastric spasm is not infrequently seen in morphinism, plumbism, general nervous states, or in timid patients who are frightened by the process of examination. With some of these spastic phenomena, such as "total gastrospeasm," for example, in which the entire stomach is irregularly contracted, we are not here concerned. Local or regional extrinsic spasms producing hour-glass deformity are most frequently seen as a cleft of the greater curvature, resembling the

incisura of a gastric ulcer. With one exception, spastic hour-glass from extrinsic causes can usually be differentiated from other forms of hour-glass. Extrinsic spasm may alter in intensity and thus change in appearance during the examination; it can sometimes be erased by steady, forceful, though not violent epigastric massage; it is often absent at a second examination; it disappears after giving belladonna (Fig. 38).

The one exception to these eliminative tests is gastric spasm arising from duodenal ulcer. The spasm ranges from a moderate incisure to a pronounced contraction, and tends to persist even after full doses of belladonna have been given, so that the observer is inclined to accredit it to a gastric lesion (Fig. 39). The puzzle is further complicated by

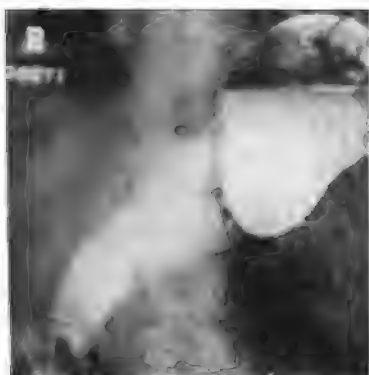


Fig. 39 (100277).—Spasmodic hour-glass stomach in a case of duodenal ulcer. The hour-glass was not present at operation because it was relaxed by the anesthesia. In our experience such spasms are not relaxed by antispasmodics.

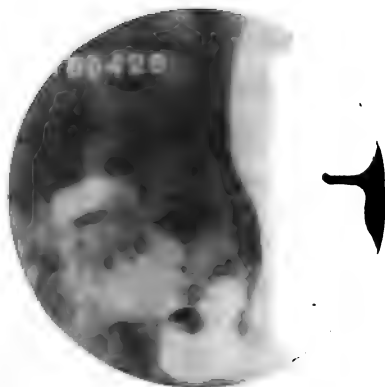


Fig. 40 (150426).—Spasmodic hour-glass stomach in a case of duodenal ulcer. This is the only type of hour-glass having an extrinsic cause not relaxed by belladonna to physiologic effect.

the fact that a duodenal ulcer and a gastric ulcer may occur in the same case. In every instance of suspected spastic hour-glass it behooves the examiner to confirm or exclude the presence of duodenal ulcer. If an ulcer is present, as shown by constant distortion of the duodenal bulb, the presumption is strong that it is the cause of the gastrosplasm, although careful search should be made for the niche of a gastric ulcer. If no duodenal ulcer is found and the gastrosplasm withstands all eliminative tests, the spastic condition is probably of intrinsic origin, thus indicating a lesion within the stomach, even though it cannot be seen (Fig. 40).

In administering belladonna to relax gastrosplasm it is emphatically necessary that the amount given is sufficient to produce the usual



physiologic effects of dryness of the throat, pupillary dilatation, etc. Our own custom is to prescribe the tincture, starting with 20 drops and repeating the dose frequently until the desired effect is obtained. Since some patients have an idiosyncrasy for the drug, it is advisable to keep them under close observation and stop its administration if untoward symptoms develop.

Atropin sulphate, injected hypodermatically in single doses of  $\frac{1}{100}$  to  $\frac{1}{50}$  grain, is preferred by some examiners. It has the advantage of permitting a second examination soon after the first, probably before the stomach is empty. We have not adopted this practice, because it is impossible to determine the necessary dose to produce a physiologic effect, and patients usually object to repeated hypodermatic injections. On the other hand, belladonna can be given by mouth without any objection from the patients and, so far as our experience goes, the results are all that could be desired.

Conflicting opinions as to the effectiveness of belladonna in abating gastrospasm are probably due to the various forms, methods, and doses in which it is given. Thus, Reizenstein and Frei state: "We must reject the accepted teaching that atropin will differentiate the spastic from the organic forms. We could never convince ourselves of a positive effect of atropin in the sense of relaxing spasm but, on the contrary, have observed an increase of it by this means." Barclay says that belladonna relaxes some spasmodic hour-glass stomachs, while it may have no effect on others that are susceptible to the effects of massage and thus prove themselves to be spasmodic. He also cites a case in which the stomach was relaxed by belladonna, and yet a healed ulcer was found at operation. Rieder, who uses the extract of belladonna, states that only a positive result is of value. Strauss has found both atropin and papaverin very unreliable in his experience. Notwithstanding the testimony of these observers, our own cases of extrinsic hour-glass stomach (barring those produced by duodenal ulcer) which failed to relax after belladonna were only those in which an insufficient amount of the drug had been given, and our own confidence in this test remains unshaken.

It is true that belladonna or atropin will not differentiate between spasmodic and organic forms of hour-glass stomachs, but they will differentiate between the intrinsic and extrinsic forms. When the hour-glass contraction is the only radiologic sign present, this test must be very carefully carried out, as otherwise the radiologists may lead the

surgeon into error. It has been our experience that any hour-glass that resists belladonna to the physiologic effect means a lesion either of the stomach or duodenum; and regardless of whether the hour-glass is present or not at operation, the surgeon will find the cause, if he looks for it.

Barclay's case of healed ulcer with relaxation of the hour-glass after belladonna is extremely interesting. We have never observed such a case. Neither have we found massage to have any effect on intrinsic gastrosplasm. At the same time the obvious fact should never be overlooked that all spasmodic forms of hour-glass stomach are relaxed by the anesthetic.

Aside from the hour-glass deformities of the stomach due to actual contraction of the gastric walls, whether organic or spastic, there are pseudo hour-glass forms, that is, certain semblances of the hour-glass form, as seen with the x-ray, which may be more or less deceptive to the untrained observer.

One of these is the elongated hypotonic or so-called atonic stomach. Hertz dignifies it by the term "orthostatic" hour-glass stomach. By reason of its tonusless walls, the stomach is lengthened and its capacity increased. Ingesta which would fill a stomach of average size accumulate in the expanded, basin-like lower pole and, with the patient standing, the dragging weight of the gastric contents causes a spindle-like approximation of the walls in the middle third. The ingesta can be forced upward by manual pressure, so as to dilate the apparent narrowing and thus prove its deception.

Somewhat similar in appearance, and perhaps related to the above, is the so-called corset-stomach, seen in enteroptotic women who are given to tight lacing. However, Groedel believes that the corset-stomach belongs to the scar hour-glass type and says: "It is anatomically confirmed that foolish tight lacing may give rise to a thickening of the serosa which shows the characteristics of a scar hour-glass." Rieder also lists it as a possibility among the acquired forms, but considers it doubtful and very improbable that tight lacing would cause a permanent hour-glass.

A third simulant of hour-glass is that produced by the imprint of a tumor outside the stomach. The indented portion of the gastric wall is usually a wide, smooth incurvation which changes appearance on manipulating the stomach.

Other causes of pseudo hour-glass stomach are, for example, strong

retraction of the abdominal wall, and the dorsal and prone position of the patient (Fig. 41). Most of these simulants can be easily eliminated by a little manual palpation behind the screen, especially while in the vertical position (Fig. 42).

Practically, then, unless the case is extraordinarily typical, it is only by a process of elimination that the several varieties of hour-glass stomach can be differentiated. First, the mere pseudo hour-glass must be excluded, and this is seldom difficult; next, extrinsic spasm from most causes can be eliminated by the various procedures mentioned, particularly the belladonna test. If the hour-glass persists after this test, the examiner may reasonably assume that the deformity is either—(1) organic of itself, (2) that it is an intrinsic spasm arising directly from



Fig. 41 (111020).—Pseudo hour-glass stomach due to strong retraction of the muscles of the abdominal wall.



Fig. 42 (147151).—Pseudo hour-glass stomach due to pressure of stomach against the spine.

a gastric lesion, or (3) that it is an extrinsic spasm due probably to duodenal ulcer.

A careful screen and plate examination of the duodenal bulb will either confirm or exclude the presence of an ulcer. If no duodenal ulcer is present, the presumption is strong that the constriction of the stomach is due to a gastric lesion, with the chances favoring ulcer or its scar, even though the niche of the ulcer cannot be seen. If a duodenal ulcer is found, it may be inferred that the hour-glass is a spastic reflex from the ulcer, although this inference is not absolutely safe, since about 11.5 per cent of duodenal ulcers occur in association with gastric ulcer. When the field has been logically narrowed to a choice between an hour-glass deformity which is organic of itself and one which is spastic but

arising from a gastric lesion, the examiner is apt to concern himself more with the nature of the cause than the manner in which the hour-glass effect is produced. In other words, he is more interested, and properly so, in deciding between ulcer, cancer, and syphilis, than in determining whether the hour-glass is due to intrinsic spasm or to permanent contraction. If the upper loculus shows a retention from the six-hour meal, or if the upper loculus sags to the left and below the cleft, or if there are irregular filling defects about the isthmus typical of cancer, the examiner may be quite confident that the constriction is at least partly organic and will be found by the surgeon. But if with a tight hour-glass constriction there is neither a retention from the six-hour meal, nor a retarded flow of the barium suspension, if no niche, accessory pocket, or filling defect is visible, and the indentation has straight, parallel borders, the contraction is probably spastic and will not be seen by the surgeon at operation.

#### CONCLUSIONS

1. Hour-glass stomach should not be considered a disease entity, but an end-result of various pathologic processes, gastric and perigastric.

2. The possibility of congenital hour-glass stomach must be admitted, although most cases reported have been questioned.

3. The roentgenogram usually shows a much deeper constriction than is seen at operation, due to the fact that the organic narrowing is exaggerated by the spasm.

4. Cases of spasmodic hour-glass, whether intrinsic or extrinsic in cause, are not seen by the surgeon, because they are relaxed by the narcosis. Therefore, if the hour-glass is the only roentgen sign present, the first thing to do is to exclude extrinsic causes.

5. Belladonna or atropin does not differentiate between the organic and intrinsic types of spasmodic hour-glass stomach.

6. Belladonna or atropin to physiologic effect will differentiate between the intrinsic and extrinsic types of spasmodic hour-glass stomach.

7. Operations have proved the organic type the most common. However, the spasmodic, when intrinsic in origin, is just as important from a diagnostic standpoint as the organic.

8. The varieties of hour-glass stomach, therefore, admit of the following subdivision:

A. Congenital.

B. Acquired.

1. Organic; constriction due to structural changes in or about the stomach. Causes: ulcer, scar of healed ulcer, perigastric adhesions, cancer, syphilis, corrosives, resection, gastrostomy, congenital (?).

2. Spasmodic (or functional); cramp of the gastric muscle without structural change. Two types: (a) intrinsic; cramp directly produced by lesions in the stomach; causes practically the same as those of organic hour-glass; (b) extrinsic; cramp indirectly produced by causes outside the stomach; duodenal ulcer, diseases of the gallbladder, disease of the appendix, neuroses, tabes, lead intoxication, morphin, nicotin.

C. Pseudo hour-glass; simulating the hour-glass form without either spasm or structural change in the stomach. Causes: contraction of abdominal muscles, pressure of stomach against the spine, tumors outside the stomach, atonic stomach, gas and fecal matter in the bowel.

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## POLYPOSIS OF THE STOMACH\*

D. C. BALFOUR

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The benign tumors of the stomach, fibromas, myomas, and adenomas, because of their relatively low incidence, obscure symptomatology, and unknown etiology, have always been of great interest, particularly from a surgical standpoint. It was, then, with considerable satisfaction that we recently added to our collection of benign gastric tumors a perfect specimen of the rarest member of the group, a gastric polyposis. The fact that this is the first time the condition has been found in approximately 69,000 abdominal sections in the clinic, 8000 of which were for gastric lesions, and that a correct diagnosis was established before operation, is sufficient to make the case most unusual.

CASE 250518.—A man, aged thirty-one, came to the clinic Nov. 8, 1918, because of "stomach trouble"; a careful elicitation of the history disclosed relevant facts as follows: In 1910 the patient began to have periods of unexplained loss of appetite; during the following five years this periodic anorexia was a great annoyance. The symptom which finally brought him to the clinic, pain with an empty stomach, first manifested itself in 1915. For a short time after its onset the pain showed some periodicity, but during the greater part of the three years it has occurred daily. The patient described the pain as a cramp beginning in the right and in the left hypochondrium, and radiating toward the midline of the epigastrium; it was not associated with burning or with the usual subjective symptoms of hyperacidity, but occurred only when the stomach was empty. He further stated that the stomach seemed to empty very rapidly, and that the period of freedom from cramps after the ingestion of food had become increasingly shorter. By frequent eating he had kept his distress at a minimum and his nutrition was practically normal. There had been no nausea or vomiting or evidence of gastric bleeding. The patient had been discharged from the army in 1917 on a diagnosis of pulmonary tuberculosis, and after five weeks in a sanatorium home treatment was maintained until June, 1918.

\* Presented before the Southern Surgical Association, Baltimore, December, 1918. Reprinted from *Surg., Gynec. and Obst.*, 1919, xxviii.

The physical examination did not disclose any abnormal findings. There were no evidences of pulmonary lesion, either clinically or by x-ray, and the Wassermann test was negative. The test-meal showed an absence of free hydrochloric acid and the presence of a considerable quantity of epithelium. This achylia explained in a measure the symptoms of which the patient complained, and considered with the character of the gastric pain and the fact that it had been continuous over a period of almost three years, practically excluded gastric or duodenal ulcer. The only clue which led to preoperative diagnosis was secured by x-ray examination. The entire pyloric end of the stomach exhibited a diffuse mottled appearance, apparently well demarcated both at the pylorus

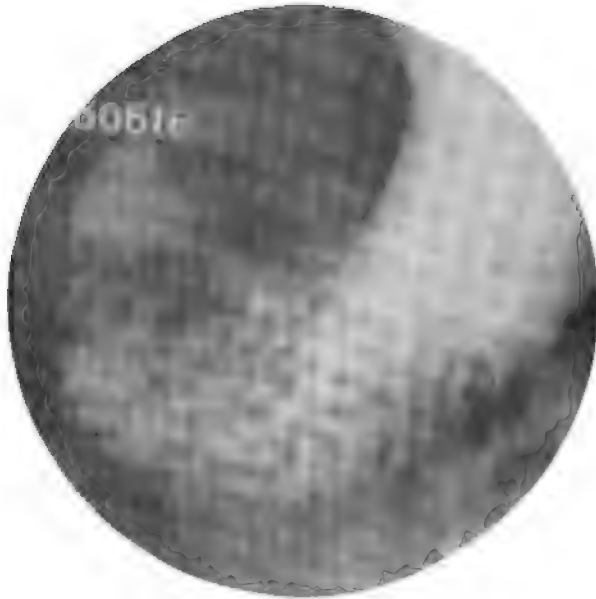


Fig. 43 (250518).—The mottled appearance (dark areas) in the radiogram are shadows due to the polyps in the stomach. (See specimen, Figs. 44 and 45.)

and at a line about four inches from the pylorus. Dr. Carman, after a re-ray, at which any possibility of complicating factors, such as the patient's having taken food before the examination, was excluded, made a diagnosis of gastric polyposis, and on this diagnosis the patient was sent to the hospital for exploration (Fig. 43).

The operation was done Nov. 19 by Dr. Sistrunk. On inspection the stomach was found to be normal in appearance; on palpation, however, a soft, doughy thickening of its wall, extending from the pylorus to a line about five inches above, was immediately evident, and although this did not give the sensation of an actual tumor, the lines of demarca-

tion were quite definite and corresponded with those apparent in the radiograph. Resection was carried out along these lines; about two-fifths of the stomach was removed. Continuity was reestablished by the method which we have found most satisfactory, that is, antecolic end (gastric) to side (jejunum) anastomosis. Immediate examination of the tumor showed a most typical example of the condition which has been described as gastric polyposis. Examination of the mucous membrane of the stump of the stomach showed that the polypoid changes did not entirely cease at the line of resection, and that small globular masses were present at various points on the mucous membrane, particularly along the summit of the rugæ, which in turn were very markedly

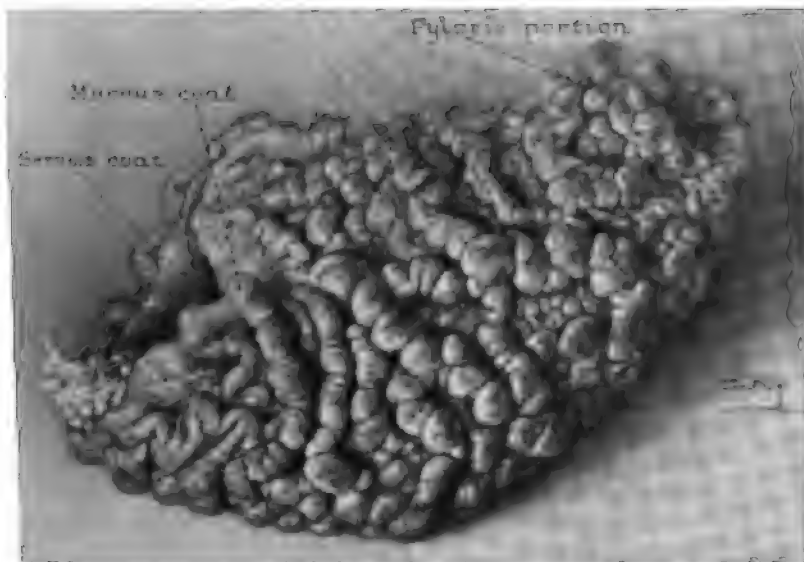


Fig. 44.—Polyposis of the stomach. (Drawing.) Stomach turned inside out.

hypertrophied. This finding created some uncertainty as to the ultimate result, but it is not unreasonable to hope that the removal of the greater portion of the diseased tissue will have a curative effect on the isolated tumors that were not removed.

Further study of the resected stomach revealed that it conformed to the type of polyposis which has been described by the French (Menetrier) as *polyadenomes polypeux*. The fresh specimen exhibited no changes except in the mucous membrane. No infiltration of the coats had taken place, and the specimen could readily be turned inside out. The mucous membrane was highly congested, and tumors of various sizes were distributed over the entire surface. These tumors were globular and were arranged noticeably in rows in the transverse axis of the stomach; the



masses were in close apposition to each other, as is shown in Miss Fry's drawing (Fig. 44). The intervening mucous membrane between the rows showed a few much smaller isolated globular elevations (Fig. 45). The great majority of the elevations were of the size of a hazel-nut, and 250 of them could easily be counted; individually they were soft and velvety to the touch, and gave no macroscopic suggestion of malignancy or of destruction of tissue. A section of the gastric wall containing a tumor examined microscopically showed the bulk of the tumor to be composed of a tremendously hypertrophied mucous membrane. No hyperplasia of glandular element was of a character to suggest malignancy. The pathologists believe the condition is not malignant; this corresponds with the generally accepted view. The patient made a very satisfactory recovery, and returned to his home Dec. 16, 1918.

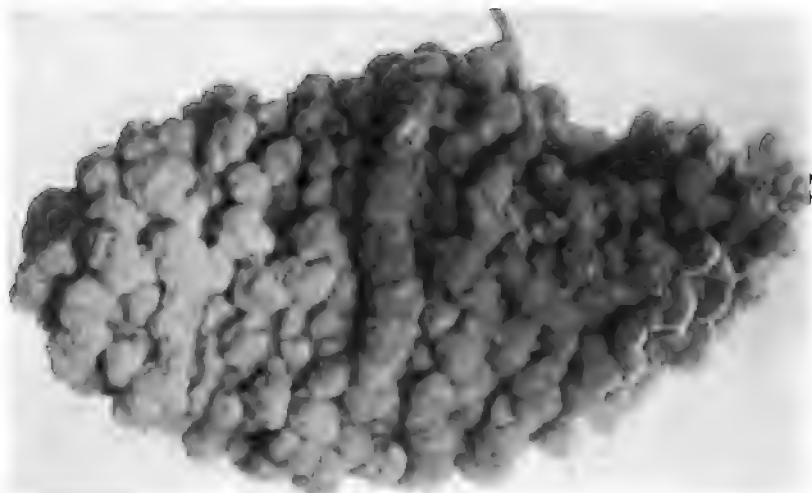


Fig. 45.—Photograph of specimen.

From a study of this case in conjunction with such cases described in the literature it would appear that gastric polyposis has sufficient characteristics to be classified as a separate entity and should not be confused with the single polyps or papillomatous masses (the latter usually malignant) occasionally found in the stomach, and to which the term gastric polyposis has at times erroneously been applied. No positive etiologic factors are known, and elaborate investigations in our own case, both before and after operation, failed to reveal any clue. It should be emphasized in this instance that the condition would have been quite unsuspected had it not been for the radiograph and its inter-

pretation. It is also of interest that in the only other similar case described in this country—that of Myer—a preoperative x-ray diagnosis was made by Carman. The age of the patient, thirty-one years, is unique because it is the earliest age at which the condition has been recognized. The accurate and early diagnosis, leading to the correct indications for treatment, is an excellent illustration of the advanced methods of diagnosis available to the clinician of to day.

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# CAUTERY EXCISION OF GASTRIC ULCER

## Further Observations on the Value of the Method \*

D. C. BALFOUR

In a previous communication<sup>1</sup> I described a method of using the actual cautery in the surgical treatment of gastric ulcer. At that time the advantages of cautery excision appeared to be sufficient to commend it, and we believed that it would prove an important addition to the operations commonly employed in chronic gastric ulcer. Since that time further experience has more than supported our early opinion of the method, its application has been greatly extended, and its value has been recognized by others, notably Scudder, Peck, and Coffey.

In the present communication I desire to make some observations, based on 214 cases of gastric ulcer, in which the cautery has been employed in our clinic, to show the advantages of cautery excision and briefly to compare its results with those of other standard methods, particularly knife excision.

The first group of cases in which the cautery was applied comprised the lesser curvature ulcers in such high situations or so extensively indurated as to make knife excision an operation of difficult technic or poor surgical judgment (Fig. 46). Under the circumstances, although gastro-enterostomy alone could be counted on to relieve the symptoms in a certain percentage of persons with such ulcers, the advantage of being able, without additional risk, to destroy the crater of the ulcer, and to sterilize the infected area by means of the cautery, was perfectly obvious. The results in this group of cases were very satisfactory, and the employment of the cautery was carefully extended so that at the present time, in a large percentage of gastric ulcers, the method appears to be the one of choice.

There are certain limitations in the method which should first be

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noted. Chiefly, that it is not applicable to those ulcers which have definitely undergone malignant change unless the lesion is irremovable because of its size, situation, or fixation, and that the procedure should be attempted only if the stomach can be sufficiently mobilized to enable safe exposure.

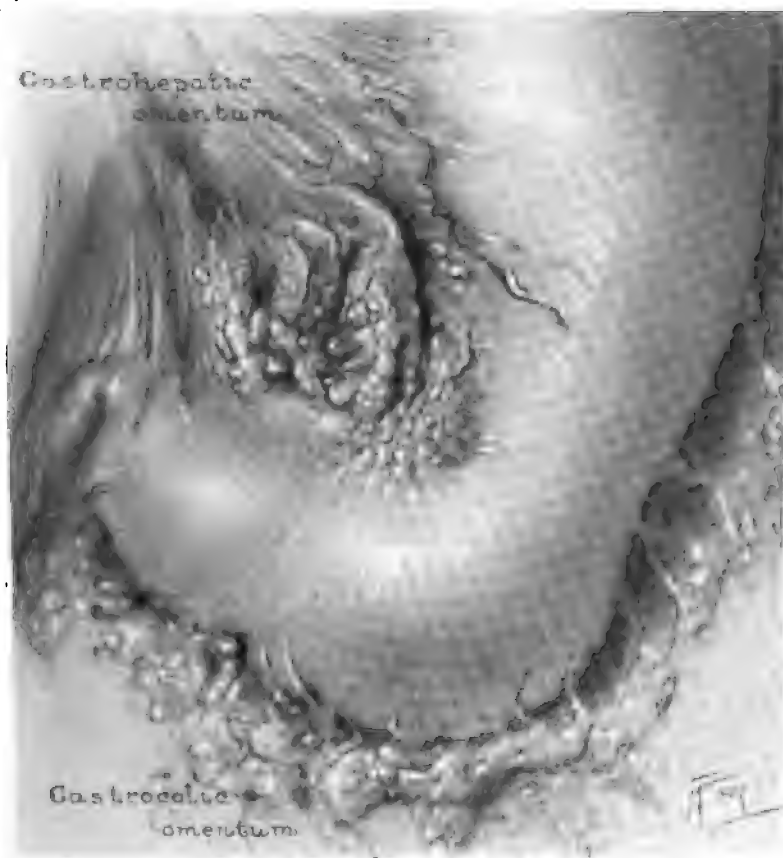


Fig. 40.—Characteristic position of stomach with an ulcer of the lesser curvature. Moderately extensive induration and thickening of the gastrohepatic omentum.

The value of the cautery in gastric ulcer seems to depend largely on two factors, namely, heat and perforation. The efficiency of heat as a sterilizing agent in infected fields is well known and widely employed. Heat has no superior in quickly and effectively destroying infectious

foci, such as cervical, buccal, or epithelial carcinomas, indolent ulcers, carbuncles, etc., and since Rosenow has demonstrated the elective localization of streptococci in gastric ulcer, the application of heat in such an infectious process is clearly indicated.

Complete perforation by the cautery point through the center of the crater of the ulcer (Fig. 47) has been made an essential in the technic because of the clinical fact (drawn attention to early by Mayo, Clairmont, and others and now generally recognized) that spontaneous and complete perforation of a gastric ulcer is, presupposing recovery from this acci-

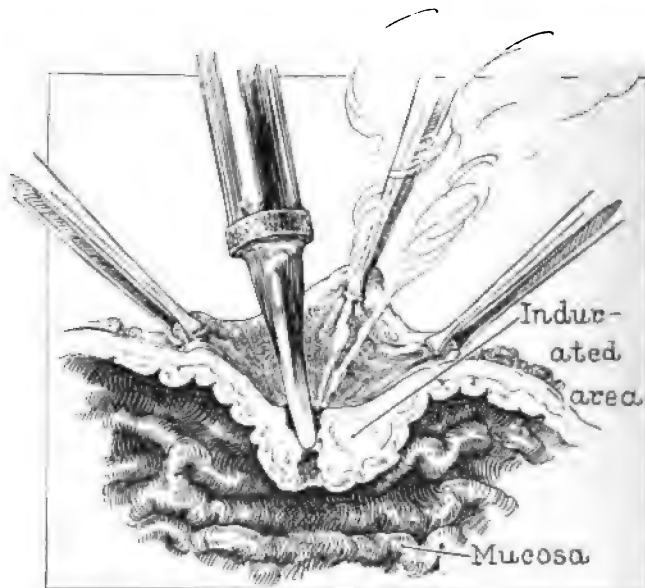


Fig. 47.—Complete perforation, by cautery, through the center of the ulcer crater.

dent, quite likely to be followed not only by the cure of the ulcer, but by the cure of the patient. The frequency with which nature attempts perforation is shown by the fact that in a very high percentage of ulcers a protected perforation has occurred by the time they come to operation (Figs. 48 and 52). The cautery technic will almost always (particularly if a thin shaving of the calloused peritoneal coat is made following the careful reflection of the indurated gastrohepatic omentum from the wall of the stomach as shown in Fig. 49) reveal a minute but very definite point in the thickened gastric wall which marks the site from which the leakage has occurred, indicating the center of the crater of the ulcer and

serving as an excellent guide for the introduction of the cautery point (Fig. 50). Cautery puncture, combining as it does the beneficial action of heat with an artificial perforation, possesses a double efficiency and it



Fig. 48.—Gastrohepatic omentum dissected off ulcer area and peritoneal surface exposed.

is undoubtedly to these two factors that the success of the method is largely due.\*

The most important advantage of cautery excision concerns its application in ulcers of the lesser curvature. In this situation the majority of gastric ulcers occur, but the high incidence has never been satisfactorily explained although certain suggestive facts are in evidence. For example, the blood-supply along the lesser curvature is much greater and of different arrangement than that on the greater curvature, a

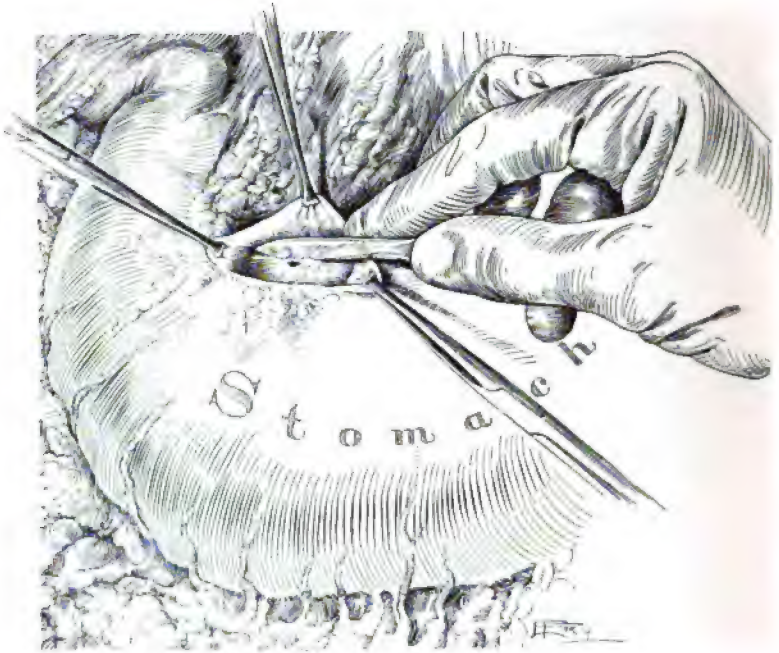


Fig. 49.—Shaving of thickened musculoperitoneal coats.

situation in which ulcer occurs with the greatest rarity; while the lesser curvature of the stomach, as Barber has recently shown, is extremely rich in vagi and sympathetic terminals, although the distribution of motor and sensory function in these terminals is not known. The significance of these anatomic characteristics is not understood, but enough evidence can be obtained by experimental methods alone to show

\* Since the original communication<sup>1</sup> Haines, of Cincinnati, has drawn my attention to the fact that perforation of a gastric ulcer by some blunt instrument had been proposed previous to that time.

that the lesser curvature of the stomach may well be given more regard by surgeons than has been afforded it in the past.

Clinical experience, too, bears out the observations of Barber and Stewart that excision of a segment of lesser curvature does definitely impair gastric motility, for it is now well known that excision alone of a



Fig. 50.—Peritoneal surface of ulcer prepared for application of cautery.

lesser curvature gastric ulcer frequently fails completely to relieve symptoms, and in order to obtain the best possible results such an excision must always be combined with gastro-enterostomy. Cautery excision, on the other hand, reduces to a minimum interference with the future motility of the stomach. Carman, in radiologic studies of stomachs following different types of operation, has recently demonstrated that



cautery excision and gastro-enterostomy gives much better motility and function and results in much less deformity than does knife excision and gastro-enterostomy. This fact can hardly be overemphasized. Notwithstanding, therefore, the good results which follow knife excision and gastro-enterostomy, if cautery puncture through the crater of the ulcer, with gastro-enterostomy, will give at least equal results, it is quite aside from advantages which will be pointed out later, a preferable method on the score alone of being less mutilating in its accomplishment.

One objection which may be raised against cautery excision is in regard to its effectiveness in those cases of ulcer undergoing malignant change, and which are otherwise excisable, but I believe it may be shown that not only is any deficiency in the cautery method more apparent than real, but that it possesses certain advantages under such circumstances. Without going into a discussion as to the frequency with which gastric ulcer becomes gastric cancer, I may offer one fact which seems to be of considerable importance from a surgical point of view. In a review, by means of a careful follow-up system, of the 1004 cases classified as gastric ulcer, in which operations were done in the clinic, I found that, in those patients dying months or years later from what was known to be gastric cancer (or, as was more often true, thought to be gastric cancer), almost invariably malignancy had been strongly suspected, the lesion was not safely removable, and a gastro-enterostomy only had been done. Investigation further showed that death eventually from gastric cancer seldom occurred in those cases in which the operative report stated gastric ulcer unqualifiedly. In other words, although the surgically untreated gastric ulcer possesses a strong liability to cancer degeneration, the gastro-enterostomized ulcer shows very little such liability. This fact discounts largely any criticism of the cautery method on the score of ignoring the malignancy factor. Such criticism is further met by the practice we follow of shaving off a portion of the ulcer base or rimming out the crater for microscopic examination before using the cautery, with immediate resection if the ulcer is malignant and operable. The fact, too, that the cautery can be used in a large group of cases in which excision is impracticable more than offsets any disadvantages of the method when used in excisable cases. The investigations of Thalhimer and Wilensky are important in this connection. They were able to show that gastric cancer, both primary and secondary to ulcer, is sharply demarcated from healthy tissue, and that local resection 1 or 2 cm. from the edge of the macroscopic evidence of the tumor is sufficient

in the majority of instances to remove all the disease. This being true means that heat used in an ulcer undergoing malignant change can, by careful application, be effectual in destroying early malignancy if no metastases are present. The destructive action of heat on the cancer cell is so positive it is not unreasonable to hope that in some of these large irremovable ulcers which have already taken on early malignant change in the ulcer base, the thorough cauterizing of the base may destroy these cancer cells and prevent an otherwise certain death from cancer later.

The actual effect of the cautery may be studied from four stand-points: (1) Experimental evidence, (2) clinical experience, (3) operative mortality, and (4) late results.

The original experiments conducted under the direction of Mann to determine the healing power of the stomach after an opening had been made by the cautery, and closed by suture, demonstrated conclusively that rapid and firm healing uniformly took place, even when the closure of the cauterized opening was more or less imperfect. The experiments carried out by Scudder and Harvey confirmed this, and they showed further that in serial sections of the line of closure following cautery excision and of that following knife excision no marked difference in rapidity of repair was demonstrated. Experimental evidence, then, has demonstrated the readiness with which healing takes place in these cauterized areas.

We have had only one opportunity of observing in man the late condition of the stomach after the operation of cautery excision. In 1915 I operated on a patient (Case 120281) for a large gastric ulcer of the lesser curvature. The induration was so extensive and extended so high on the lesser curvature that not only was excision quite contraindicated, but the possibility of a second ulcer was considered. Only one crater could, however, be determined. This, after its exact location on the peritoneal side, was exposed by mobilization, was punctured with the Paquelin and thoroughly cauterized, the opening closed, and a gastro-enterostomy done (Fig. 51). The patient made a good recovery and returned home. Later he contracted lobar pneumonia followed by empyema, and he returned to the clinic acutely ill, where, notwithstanding prompt and efficient drainage, he died. At necropsy the stomach was the organ of particular interest. In spite of the great induration along the lesser curvature at the time of the operation, there was no evidence that any pathologic condition had existed or that any operative work had been

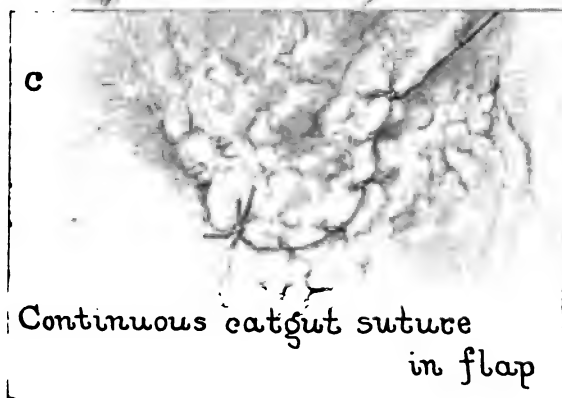
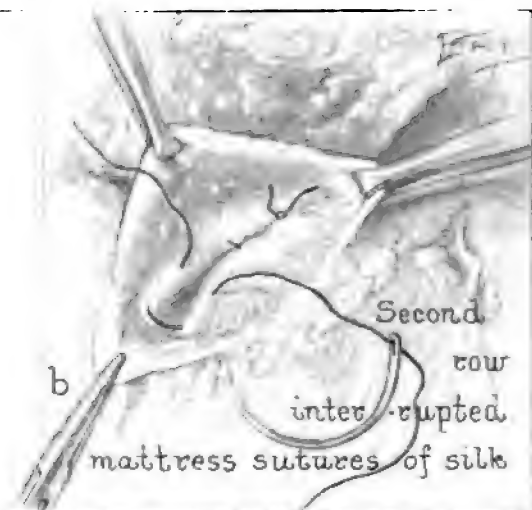
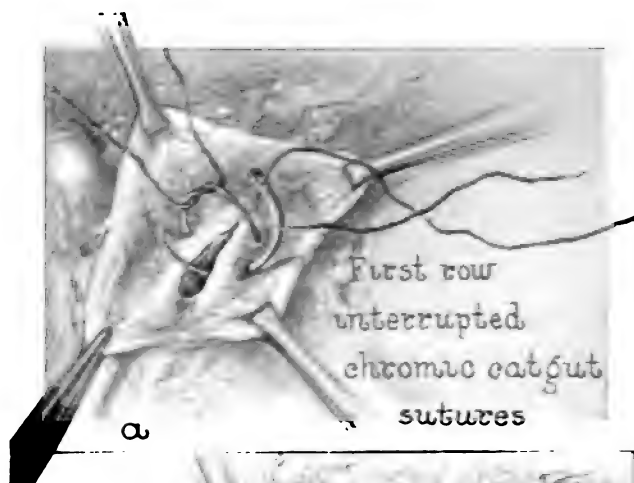


Fig. 51.—Method of closing cauterized opening. a, First row, chromic catgut sutures; b, second row, silk mattress sutures; c, third row, continuous catgut sutures.

directed toward the lesser curvature. The gastro-enterostomy was normal. These findings were extremely gratifying inasmuch as the result was obtained in a case in which knife excision could not be done, and in which heretofore a gastro-enterostomy alone would have been made.

The low operative risk of cautery excision and gastro-enterostomy is shown by the fact that in the 186 cases in which this was the major operation there were two deaths, giving a mortality in the series of only 1 per cent. The necropsy findings in each of these two cases demonstrated that the field of operation was in perfect condition; the cause of death in one being pulmonary embolus on the eighth day and in the other pneumonia on the twentieth day. In comparing these statistics with those of knife excision and gastro-enterostomy we find that in the 89 cases in which operation was done by this method 3 deaths occurred—a mortality of 3.3 per cent.

The convalescence of the patients in whom cautery excision and gastro-enterostomy are done is uniformly smooth, and the clinical post-operative course bears out Carman's observation that better gastric motility is attained than in those operations (particularly excision of a V-shaped segment in the lesser curvature) which entail greater damage to the musculature of the stomach. The reports of the late results, as they come in, are most favorable. Of the 61 cases in which the cautery was used in 1914-1915, we have positive information in 55. In this number there have been 4 deaths from all causes since operation, 2 already mentioned following operation, the other 2 of unknown causes at their homes in the three or four years after leaving the Clinic. Of the remaining 51 patients operated on in the two years, 80 per cent have reported a satisfactory result (cured and greatly improved), 18 per cent were improved in the sense of amelioration of symptoms present previous to operation, while in no instance did a patient report that he had not obtained relief from the operation.\* The cases of knife excision and gastro-enterostomy in this period show corresponding figures of 70 per cent and 15 per cent while 15 per cent of the patients state they are no better. These figures of mortality and late results have more force when it is remembered that the knife excision cases are essentially selected, inasmuch as this operation is done only when conditions are favorable, while the cautery is often employed in the very case in which

\* One patient (2 per cent) after five months of relief developed similar symptoms and returned to the Clinic. Re-examination disclosed indications of a gastrojejunal ulcer and operation confirmed such a diagnosis and corrected the difficulty.

excision is unwarranted because of the size, fixity, and situation of the ulcer.

As to the relief of special symptoms, I would draw attention to the very important fact that in not a single instance has there been a recurrence of hemorrhage from the ulcer following operation by the cautery

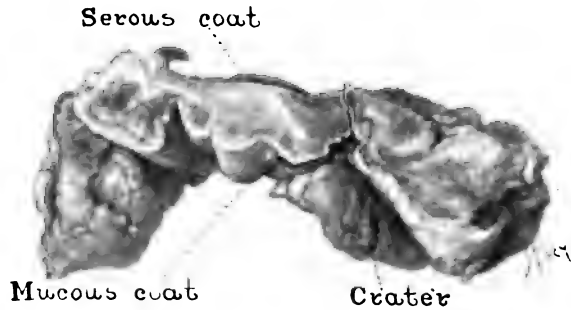


Fig. 52.—Cross-section of ulcer, showing tract of perforation.

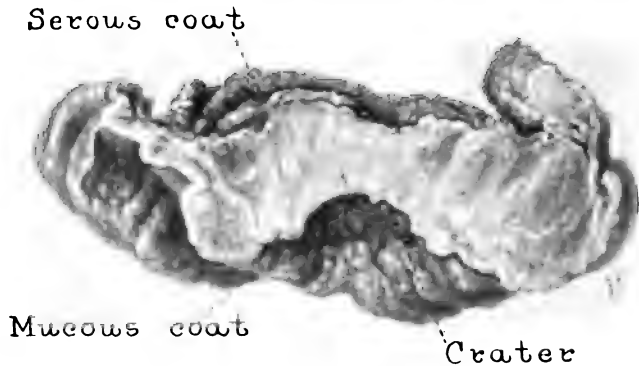


Fig. 53.—Half section of ulcer showing extensive induration.

excision method. It is well known by surgeons of experience that operations for gastric or duodenal ulcers which have been associated with bleeding do not always obviate later gastric hemorrhages. That bleeding has not recurred thus far in any of our cases following the use of the cautery has been a source of considerable satisfaction. One of the

primary purposes also of the cautery was to lessen the likelihood of immediate postoperative hemorrhage, and in this the method has fulfilled expectations.

From a technical standpoint, excision by cautery accomplishes much in a simple way which is not true of excision by knife. It is a common observation that the induration around an ulcer is out of all proportion to the size of the crater (Fig. 53), and that excision sacrifices, along with the actual infected area, the protective induration with which nature attempts to wall off the infectious foci which exist in the crater. Our experience with the cautery has shown that this wide excision is just as unnecessary as it is in the treatment of infectious foci elsewhere, and that the indurated area can be restored to a healthy condition by destruction of the crater and thorough heat sterilization of the surrounding tissues as the cautery is held in the punctured crater. The heat is an important factor and would destroy adventitious cells for from 1 to 2 cm. in every direction. The utility of the cautery is particularly well demonstrated, therefore, in greatly indurated ulcers (the actual size of the crater is rarely greater than a twenty-five-cent piece), which can be safely mobilized. Knife excision under such circumstances, necessitating as it does complete removal of the indurated area, is an unsatisfactory procedure if some substitute is available which will accomplish as much without unnecessary sacrifice of gastric wall.

The cautery, therefore, has been found of very great usefulness in gastric ulcer. Although I have considered in this paper only the 186 cases of gastric ulcer in which cautery excision was combined with gastro-enterostomy, we have also used it without any other operative procedure, as well as with various types of gastroplasties and pyloroplasties. In a few cases we have employed it to destroy small duodenal ulcers, particularly those associated with hemorrhage, and it would appear that in such cases the method has particular usefulness of application.

The apparent advantages of the method may be summarized as follows:

1. The cautery efficiently destroys the focus of infection in gastric ulcer without the sacrifice of nature's protective induration surrounding the ulcer crater.
2. It may be applied in a large percentage of gastric ulcers.
3. It entails a minimum of operative risk.
4. Clinically and radiologically better motility and function are shown than follow knife excision and gastro-enterostomy.

5. It has a particular efficiency in obviating early and late post-operative hemorrhage.
6. The late results are better than those obtained with any other method.
7. It can be used in cases in which no other means of direct attack on the ulcer is justifiable.
8. It is probable that in gastric ulcer cautery, like knife excision, should always be combined with gastro-enterostomy.

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# THE TREATMENT OF PEPTIC ULCER BY GASTRO-ENTEROSTOMY\*

C. H. MAYO

In the study of digestion as a necessary function in the maintenance of life one comes very close to the fundamental question of life itself. The assimilation of the essential elements by plant life, singly or in combination, or in animal life by the process of the single cell, or the action of an organ, is all equally interesting and almost equally marvelous. The various activities of the cell are solved apparently only here and there, and, while many of our leaders in research have undertaken the study of the special problems with a preconceived notion of the subject and its solution, their work is frequently biased and they often bridge serious difficulties by theory.

Many of the great discoveries of medical science have been developed by our army medical officers; the work was often started as a bit of scientific research to make a change in the monotonous routine in army posts. William Beaumont started the first practical investigation of human digestion and published his observations in book form in 1833. They were based on an injury to the stomach through the diaphragm of a French Canadian, Alexis St. Martin, from which injury a high, permanent gastric fistula was formed. It is of interest that much of this work was done at Mackinac, Michigan, at Plattsburg, New York, at Prairie du Chien, Wisconsin, and last, at Washington. Beaumont's work has been the introduction to, as well as the basis for, nearly all investigations in regard to gastric digestion. Among the many students of this subject Pavlov, of Russia, who based his studies on experimental fistulas developed in animals, has been one of the most prominent. Cannon, of Boston, has also won recognition by work on the mechanics of the stomach and the intestines.

The mechanism of the stomach by means of which the digestive

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fluids are produced is very delicately developed for the work to be accomplished. In this respect it is much more efficient than if it were under voluntary control, although it may quite often be stimulated and upset in its function by psychic action. By working on the theory of cell activity and its control by types of food, Sippy and his followers, taking advantage of the action of fats in delaying digestion and reducing the acidity with the additional administration of alkalis, have developed a very good system of control of the acids by variation in diet and by frequency of administration of food. Unquestionably, much may be accomplished along this line. I would take issue, however, with the statement that gross gastric ulcers are comparatively frequent or that they are readily healed. Such ulcers are rarely multiple, and the heavy induration backing the ulcer prevents healing by preventing approximation of the mucosa. Ulcers of the stomach must be destroyed by perforation, by cautery, or by excision to accomplish such approximation. I do not believe that true ulcers exist without evidence on the surface or in the tissue, although surface ulcers, as described by Beaumont, aphthous in type, do occur in the stomach mucosa as well as in the mouth, and heal without leaving a scar.

Gastric and duodenal ulcers are probably the result of local thrombi from an infection by a certain group of streptococci which grow in an acid field. Such ulcers are found four times as often in men as in women of every walk of life, in every country, and under every condition except that of a non-acid stomach. They are not caused in man by traumatism of the mucosa through bones or foreign bodies, such as fowls naturally take as aids to digestion. About 80 per cent of gastric and duodenal ulcers appear in the first portion of the duodenum, in which each bolus of acid chyme remains until neutralized. Occasionally the bacteria are undoubtedly carried in the blood-stream from a local focus, and at times bacteria enter the chyle duct from the intestine, but do not attack the mucous membrane, except as infarcts in its capillary circulation, in the rear, so to speak, and the area involved is at once attacked by the pepsin in an acid medium. Rosenow, in his research work, produced gastric ulcers in a very large percentage of instances by injecting into the blood-stream of animals bacteria derived from gastric ulcers.

The patient who is suffering from gastric ulcer describes attacks of stomach trouble of a few weeks' duration, which alternate with periods of a few to many months of good health; the attacks, however, become more frequent or continuous as the condition becomes chronic. The

patient speaks of pain; of burning on an empty stomach three to four hours after eating; of sour, burning eructations in the night; of food ease, and later soda ease, because of the dilution or neutralization of the acid. The passage of food over the ulcer is always a relief. The acid and pepsin-covered ulcer in the food empty stomach or duodenum is the cause of pain, as the stomach, when empty of food, often contains a quantity of gastric secretion induced by pyloric spasm. It is evident that duodenal alkalis do not respond to gastric acids, as do the pancreas and liver.

Occult blood is of but little aid in making the diagnosis of gastric ulcer. True hemorrhage occurs in 25 per cent of cases. Close questioning of the patient concerning the appearance of bloody or dark stools may give a much higher percentage than this. The x-ray gives very conclusive evidence in about 95 per cent of cases; failures in diagnosis are usually due to reflexes from the gallbladder or appendix to the stomach.

Sippy has done much to establish a basis of medical treatment of ulcer. He has shown that pepsin must have free acid above five points (the higher the better) in which to work. His principle of treatment in an attack is, therefore, to reduce the acid content by dilution of food or by neutralization with alkalis every hour during the greater part of the day. Milk and fats dilute the acid and delay digestion, with a gradual reduction of acidity.

It is just as much a fallacy to say that a peptic ulcer is always cured or healed after an attack is over, as to consider an ulcer of the leg healed after the painful ulcer has become quiescent. The higher the free acid, the more active the pepsin; combined acids, as in cancer, activate pepsin but slowly; the pain in the latter cases is therefore due to peristalsis. Whatever the degree of acidity, neutralization must occur in the area of Brunner's glands in the upper portion of the duodenum. The circular muscle of the duodenum about the region of the common duct holds each acid bolus in the first  $2\frac{1}{2}$  inches of the duodenum until the mass, regardless of the number of ineffectual peristaltic waves in the pyloric portion of the stomach, is neutralized by duodenal secretion to prepare for the alkaline digestion. When the mass is neutralized and alkali touches the pyloric ring, the next bolus will be delivered to pass through the same process. The neutralized chyme passes on to be acted upon by the pancreatic juices and the bile fluids, the latter aiding in emulsifying fats. Only within this neutralizing field of the duodenum can an ulcer occur. The duodenal secretion is stimulated less by gastric

juice than by food. Eating stimulates the essential digestive preparation, which is alkaline; the acid is convenient and essential for the preparation of certain foods, but it is not essential to life. The acid activates the secretin in the mucous membrane of the upper intestine, although secretin appears as an activating agent without acid, and thus stimulates the pancreas to secretion. We often see patients who complain but little while under observation, yet who show a non-acid stomach for months and years. Some few persons, supposed to possess non-acid stomachs, have a thirty-minute period of acidity within the hour after eating. Those with non-acid stomachs have a relaxed pyloric sphincter, which may be seen when of necessity the bile is delivered by operation into the stomach. Persons with hyperchlorhydria do not have spells of trouble; their trouble is continuous and is caused by a spasm of the pyloric sphincter with a retention of many cubic centimeters of acid and gastric juice, and occurs on a food-empty stomach. They are relieved by taking soda or food; even a few peanuts or kernels of popcorn are a mucus stimulant, and develops the duodenal secretion, without which the alkali will not bring about the relaxation of the pyloric muscle and the relief sought. A lack of balance between the gastric acids and the duodenal alkalis of digestion is probably the cause of gastric ulcers, as a biochemic factor allergic to a group of acid-growing streptococci.

Paterson has shown that the acids in the stomach are lowered about 30 points after gastro-enterostomy. After the stomach has been emptied of food, the duodenal secretion ceases and the pyloric spasm ensues; some bile and the alkaline intestinal secretion are then found mixed with and diluting the acid secretion remaining in the stomach. After gastro-enterostomy for duodenal ulcer the greater part of the food will pass through the new opening for some weeks; later, after healing is complete, through the natural peristaltic efforts of the stomach, the new outlet divides its work with the pylorus. Healing follows upon the lowering of the acid media and a chemical change occurs in the natural environment of the bacteria, which enables natural immunity agents to deal with them and their results. The patient makes use of his own drug-store for neutralization, so to speak, and the effects of the spasm of the pylorus are overcome by the new opening. An ideal gastro-enterostomy would make possible a trap-door which would close when food was taken, and open after all food had left the stomach and duodenal secretion had ceased; this would permit gastric secretions to pass through as well as to be diluted through its opening; thus the effects of spasm of the

florus would be overcome until food is again taken and duodenal secretion again occurs.

Rarely after gastro-enterostomy a new crop of bacteria, or a change in the type of the old, infects the new opening, and a gastrojejunal ulcer appears. Silk suture material may, in some instances, be a cause of the induration and irritation about the ulcer area; in 80 per cent of such cases seen by us the silk suture in the field was exposed to the gastric juice from one to four years after operation.

Perforation of a gastric or a duodenal ulcer occasionally occurs, but death does not usually follow, because protective adhesions develop to prevent general infection.

Thirty-eight per cent of all cancers found in man are in the stomach. They are less frequent in women than in men. Because malignant growth occurs in acid fields, the destruction of gastric ulcers should be undertaken as a prophylactic measure. Since ulcers of the duodenum occurring in a naturally alkaline field rarely develop into cancer, extensive operation is not necessary as a preventive.

In peptic ulcer of the stomach and duodenum gastro-enterostomy becomes a mechanical agent in the overcoming of biochemic conditions. The modern treatment of peptic ulcer of the stomach and duodenum by gastro-enterostomy is so satisfactory a relief that a discussion of its development may be an aid in establishing measures of diagnosis as well as of treatment.

The early surgical treatment of ulcer by suture anastomosis was employed only in operations of necessity, in acute perforation, in obstruction, chronic and increasing, and in cases of severe (continuous or recurring) hemorrhage.

Various mechanical devices have been invented, partly as an aid and partly to share with the operator the credit for the results, which were frequently good but often bad. Nicholas Senn advanced Connell's bone plate; next the late J. B. Murphy produced his mechanical device, the button. To the Murphy button should be credited a large share in the development of intestinal surgery. The McGraw elastic ligature enjoyed a brief period of experimental use. Later came the Mayo-Robson bone bobbin, which served as an absorbable framework over which anastomosis of a definite size could be made, but these were not extensively employed. The suture method had gradually developed, and it is displacing all other methods. The button is still occasionally employed in special conditions.

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First silk, then silkworm-gut, Pagenstecher linen, plain linen, and, later again, silk, followed last by chromic catgut, have displaced one another as popular suture materials.

The first operations were anterior gastro-enterostomies by the long loop of jejunum drawn over the front of the transverse colon and attached to the anterior wall of the stomach with the bowel turned for isoperistalsis. If there was marked obstruction, the operation gave great relief. Later came the posterior attachment; by this method the stomach was united to the bowel through a small rent made within the loop of the middle colic artery in the mesentery of the transverse colon. Then commenced the problems of gastro-enterostomy, for, as knowledge of the symptoms of ulcer and improvement in the technic of its treatment increased, the operation was no longer one of necessity only: it became one of expediency.

The fact that the stomach is an organ largely affected by reflex disturbances from the eyes, the mind, the pelvis, the appendix, the gall-bladder, and the nervous system was often overlooked, and operations for ulcer, as based on symptoms, were common. The long posterior or nine-inch loop often developed vicious circles; to avoid these the loop was united proximal to the gastro-enterostomy by suture or button. the Y or Roux operation was devised, the pylorus was excised and its ends closed, or it was obstructed. It was believed that if food left the stomach in a new way the gastric ulcer was relieved even when the pylorus was normal and without obstruction. The operation was changed by a few surgeons to plastic methods of enlarging the pylorus: the Heinecke-Mikulicz operation, the Finney operation, and various plastic gastroduodenostomy methods were devised which overcame obstruction due to spasm of the pylorus without changing the acidity. At this time the short loop and, later, the no-loop methods were devised. Most surgeons became aware that gastro-enterostomy was an added burden to the patient with gastric reflex disturbance, and insisted on seeing the ulcer before operating on the stomach; or, if the ulcer could not be seen, rather than make an unnecessary gastro-enterostomy, they investigated abdominal sources of gastric reflex for relief. The twist in the bowel for isoperistalsis, as made in the long-loop anterior operation, had been preserved in the posterior methods, and while it made no difference in the original method, the splenic loop, continuing the bowel to the left after crossing the spine, was twisted back upon itself, and in a truly short loop tended to obstruction in a certain percentage of cases.

This led to more methods of blocking the pylorus by suture, by folding ligatures, round ligament, fat, fascia, and excisions, which were intended to force the stomach to utilize the new outlet. All these measures were unnecessary from every standpoint, unless an ulcer on the gastric side of the pylorus, as a tumor which potentially might develop cancer, should be removed. It was soon learned that gravity played no part in the emptying of the stomach, that it would remain dilated unless it was relieved by its own peristaltic efforts, and that these efforts could not overcome obstructive conditions in the intestine. If the latter were present, the stomach would dilate and give trouble until the obstruction was relieved. Two other conditions would also cause it to dilate: first, injury of the innervation from wide excisions of ulcers on the lesser curvature, and second, interference with the mesenteric circulation, which often could be relieved merely by turning the patient on the left side or upon the face. The dilatation from paresis required lavage of the stomach, often over a period of from two to five weeks, until innervation was restored. As excision is now made by the Balfour cautery method, which destroys only the ulcer, paresis seldom occurs.

The best type of gastric cases for surgery is that in which every method of medical treatment has failed, or the patients have become tired of the rigid diet and care which are necessary to relieve or to prevent relapse. Such patients greatly appreciate the relief obtained through gastro-enterostomy, and the ability to return to work with the diet that can be obtained by them in their station and environment.

# A STUDY ON THE ETIOLOGY OF CHOLECYSTITIS AND ITS PRODUCTION BY THE INJECTION OF STREPTOCOCCI\*

R. O. BROWN

In 1914 Rosenow, by making cultures from the emulsified wall of the gallbladder of selected cases, found streptococci in most instances, and he reproduced cholecystitis in animals by injecting intravenously the freshly isolated organisms. The work recorded in this report is similar to that of Rosenow, except that all gallbladders removed in operations in the Mayo Clinic, regardless of the degree of pathologic changes, were cultured.

The tissues were cultured as soon as possible after their removal, every effort being made to prevent contamination. Immediately before emulsifying the tissues were thoroughly washed in large volumes of physiologic sodium chlorid solution. They were then ground in mortars within sterile air-chambers or in a hood, the air of which was washed by means of steam from a sterilizer fastened to the end of the hood. The operator wore gloves and sleeves which, with the materials used, were sterilized in the sterilizers opening into the hood.

The emulsions thus made were inoculated in varying concentrations into tall columns of dextrose brain broth, blood broth, litmus milk, ascites dextrose broth, ascites dextrose agar, and dextrose agar. Krumwiede plates of dextrose blood agar and plain blood agar plates were poured also. The cultures were studied at the end of twenty-four hours, but those that were negative were examined daily for a week.

Altogether cultures were made from 70 gallbladders and 4 ulcers. At first cultures were also made from the contents of the gallbladders, but because of the large number of negative results, regardless of the findings in tissues, this was abandoned.

The duration of the symptoms in the cases studied ranged from three months to thirty years. The pathologic changes ranged from slight to

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marked thickening of the walls. The results of the cultures are summarized in Table 1:

TABLE 1.—RESULTS OF CULTURES

MATERIAL CULTURED	NUMBER	PER CENT SHOWING		
		Streptococci	Colon Bacilli	No Growth
Gallbladders showing slight changes . . . .	50	30	18	58
Gallbladders showing marked changes . . .	20	75	15	25
Ulcers . . . . .	4	100	0	0

In the gallbladders showing slight changes 30 per cent only yielded streptococci, in contrast to 75 per cent in those showing marked changes. Moreover the gallbladders in which marked changes existed showed the larger number of colonies. Some of these contained countless numbers of organisms, while those showing slight changes, with few exceptions, contained a small number. Of the latter, 58 per cent gave no growth, while only 25 per cent of those showing marked changes gave no growth. In the cases showing slight changes colon bacilli were isolated in pure culture from 12 per cent, and in combination with streptococci from 6 per cent. The entire 15 per cent of those with marked changes contained both colon bacilli and streptococci.

Some of the organisms, when first isolated, produced opaque, indifferent colonies on blood agar, and microscopically were grouped in diplococcus forms with little or no chain formation. Further study, however, proved them to be streptococci. In this connection an interesting observation was made. From one of these cases, showing a pure culture of opaque gray staphylococcus-like colonies, two strains derived from a single colony were studied. The one kept on blood agar alternately aerobically and anaerobically became a green-producing streptococcus. The other, planted alternately in dextrose brain broth and on aerobic and anaerobic blood agar slants, developed hemolytic powers.

The different strains varied somewhat in their fermentative powers. Of the 18 studied, all fermented dextrose, lactose, and maltose, 3 raffinose, 4 mannite, 10 salicin, and 7 inulin. One strain after a single animal passage had its fermentative powers changed, but it was still agglutinated, the same as the original strain.

Microscopic examination of the gallbladders failed to reveal bacteria when negative cultures were obtained, but bacteria were found con-



sistently when the cultures were positive. Organisms were found in the lesions produced in rabbits, but were not found in normal tissue. At the suggestion of Dr. E. S. Judd, microscopic examination of liver sections which he removed were made in 10 cases. Interlobular cirrhosis was found in 6, no change in 2, and a bile-duct involvement in 2. The livers which were normal and those showing fibrotic changes were found in cases in which the gallbladders showed marked and slight changes, while in those showing cholangitis there was little or no change.

#### ILLUSTRATIVE CASES AND ANIMAL EXPERIMENTS

**CASE 55.**—A man, aged thirty-four years, for the past two years has had gastric symptoms. Pains were aggravated by food, and soda gave no relief. He was operated on August 20, 1918. The stomach was normal; the gallbladder showed slight changes and contained one large stone; the appendix showed slight changes; these two organs were removed. About 3 c.c. of the emulsion of the fundus of the gallbladder were cultured.

August 21: All the cultures showed indifferent streptococci in pure form. Five c.c. of the dextrose brain broth culture were injected intravenously into Rabbit 1662.

August 22: The rabbit appeared to be well.

August 23: The rabbit appeared to be well; it was chloroformed. and the gallbladder was found greatly distended with watery bile; the walls were edematous. The stomach, spleen, kidneys, appendix, lungs, and heart were normal. No other lesions could be found.

August 24: Cultures made from the blood of the rabbit were negative, while those from the bile and gallbladder showed countless numbers of the injected streptococci.

August 26: Cultures were made from the pus expressed from the patient's tonsils.

August 27: The blood agar plate cultures showed indifferent and green-producing streptococci and colon bacilli. The dextrose brain broth cultures from the tonsil, containing both streptococci and colon bacilli, were injected intravenously into Rabbits 1682 and 1683.

August 28: Both animals were found dead. Autopsy showed marked postmortem changes, but no evidence of specific localization. Five c.c. of the dextrose brain broth culture made from one of the indifferent colonies of streptococci was injected intravenously into Rabbit 1686.

August 29: The rabbit seemed well.

August 30: The rabbit seemed well; it was chloroformed, and the gallbladder was found edematous and distended. There were several small hemorrhages and white necrotic areas in the fundus. No other lesions were found.

August 31: Cultures from the blood were negative. Cultures from

the gallbladder showed streptococci in pure form. Microscopic examination of gallbladder revealed streptococci in the tissues.

The primary cultures of three other cases of cholecystitis were injected intravenously in rabbits. The gallbladders in two of these showed marked changes and cholecystitis developed in each of the two rabbits injected. The streptococcus was recovered from the gallbladders in each, while the blood was sterile. The third strain isolated from a gallbladder showing chronic changes showed no definite localization.

**CASE 58.**—A man, sixty-eight years of age, had had intermittent attacks of pain in the region of his stomach for the past thirty years. The pain was worse in the afternoon and was not affected by food. He was operated on August 21, 1918. An ulcer, 1.5 cm. in diameter and 4 mm. deep, with markedly indurated walls, was found on the lesser curvature of the stomach, about five inches from the pylorus. The ulcer was excised.

**August 22:** Cultures of the emulsified ulcer showed streptococci in pure form. Five and 8 c.c. of the dextrose brain broth culture from the ulcer were injected intravenously into Rabbits 1675 and 1676 respectively.

**August 23:** Rabbit 1675 seemed well. Rabbit 1676 was found dead. The cardiac end of the stomach showed 14 punctate hemorrhages with surface erosion. There were no other lesions except coccidial abscesses in the liver and in the inguinal region.

**August 24:** Cultures from the blood and bile were negative. Cultures from the lesions in the stomach gave streptococci in pure form. Rabbit 1675 seemed well. It was chloroformed, and the cardiac end of the stomach showed several punctate hemorrhages with beginning ulceration. Other lesions were absent.

**August 25:** Cultures from the blood and bile gave no growth. Cultures from the affected areas of the stomach gave streptococci in pure form.

**August 26:** Cultures were made from the pus expressed from the patient's tonsils.

**August 27:** The blood agar plate cultures contained colon bacilli and green-producing streptococci. Three c.c. of the dextrose brain broth culture containing colon bacilli and streptococci from the tonsils were injected intravenously into Rabbit 1681.

**August 28:** The animal was found dead. There were marked post-mortem changes, but no evidence of localization.

**August 29:** Cultures from the bile were negative. Cultures from the blood showed countless numbers of green-producing streptococci.

One other rabbit was injected with streptococci from an ulcer. It showed definite lesions in the stomach, as did the others. Cultures made from the lesions showed streptococci, while those from a normal portion of the stomach were negative.

To determine further the specificity of the organisms isolated, serums were obtained from the cases cited for agglutination purposes.

TABLE 2.—RESULTS OF AGGLUTINATION EXPERIMENT

SERUMS	DILUTIONS OF SERUMS	TONSIL (Case 55)	GALL-BLADDER (Case 55 after one animal passage)	ULCER (Case 58)	ULCER (Case 58 after one animal passage)	ULCER (Case 75)
Case 55 (cholecystitis) . . . . .	1-2	0 cloudy	++	+	0	0
	1-4	++	++	+	0	0
	1-8	++	++	+	0	0
	1-20	0	++	0	0	0
	1-100	0	+	0	0	0
	1-500	0	0	0	0	0
Case 58 (ulcer of stomach) . . . . .	1-2	0	++	+	+++	0
	1-4	0	0	++	+++	++
	1-8	0	0	++	++	++
	1-20	0	0	++	+	0
	1-100	0	0	+	0	0
	1-500	0	0	+	0	0
Normal control . . . . .	1-2	0	0	+	++	0
	1-4	0	0	+	+	0
	1-8	0	0	+	0	0
	1-20	0	0	0	0	0
	1-100	0	0	0	0	0
	1-500	0	0	0	0	0
NaCl control . . . . .	1-1	0	0	0	0	0

As shown in Table 2, the serum of the patient with cholecystitis agglutinated both the strains from the tonsil as isolated, and the strain from the gallbladder after one animal passage, but failed to agglutinate the ulcer strains. The serum of the patient with ulcer, on the other hand, agglutinated the homologous ulcer strain as isolated and after one animal passage, and the strain from another case of ulcer, but not the cholecystitis strains. The normal human serum had little or no agglutinating power over any of the strains.

#### SUMMARY

By making cultures of the emulsified tissues of gallbladders or adjacent lymph-glands, streptococci are found to be the chief microorgan-

isms associated with cholecystitis. The direct etiologic relationship of the streptococci is established by their presence, often in numbers proportionate to the degree of gross and microscopic changes, by their having elective affinity for the gallbladder of animals, and by the specific agglutinating power of the serum of the patient from whom isolated. The elective affinity for the gallbladder of animals of the strains from the tonsils indicates strongly that cholecystitis is commonly a blood-borne infection from a focal source.

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## THE FUNCTION OF THE GALLBLADDER. AN EXPERIMENTAL STUDY\*

F. C. MANN

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A few years ago, at the suggestion of Dr. E. S. Judd, and in collaboration with him, I removed the gallbladder from various species of animals and studied the effect of such a procedure on the remaining portion of the biliary tract. Certain definite facts were ascertained by this study.<sup>1</sup> I shall now make a preliminary report of other researches on the problems suggested by the former investigation. The purpose of this work has been to obtain facts in regard to the functional significance of the gallbladder.

The anatomic region occupied by the biliary tract is one of the most important in the body from the physiologic, and especially from the pathologic, point of view. A large percentage of operations on man have for their purpose a correction of pathologic conditions found in this area, and for this reason any increase in our knowledge of the function of the gallbladder is of value.

There are very few structures in comparative anatomy which show a wider range of variation than is shown by the different component parts of the biliary tract from each other. The exact anatomic arrangement in one species is rarely duplicated in another species. The gallbladder may or may not be present. This anatomic difference is observed even in very closely related species. In some species two ducts may be present. In other species small hepatic ducts enter the gallbladder directly. In at least one species the gallbladder is present in some individual animals and absent in others. The formation of the common duct is rarely the same in different species. The cause or significance of these marked variations in the comparative anatomy of the biliary tract never has been determined.<sup>7</sup> The problem has not been solved by embryologic studies.<sup>18</sup>

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Many theories have been developed concerning the function of the gallbladder, varying in the functional importance which they attach to the gallbladder from the one which implies that the organ is perfectly useless<sup>17</sup> to that which attributes to it the production of something necessary for the well-being of the organism. In general, each theory of the function of the gallbladder may be grouped into one of three divisions: (1) As a reservoir for the storage of bile; (2) as a secretory organ, elaborating and adding something which is of importance either to the general body economy or to the mechanism of bile expulsion or its chemical action, and (3) as a regulator to the flow of bile.

The positive statements which may be made in regard to the function of the gallbladder are very meager. It is known that the small amount of smooth muscle contained in its walls is under the usual double nervous control observed in the other viscera. It receives fibers from both the vagus and sympathetic nerves. The splanchnic nerve seems to be predominantly inhibitory in action, while the vagus is mainly motor.<sup>2, 11</sup> The gallbladder undergoes rhythmic contractions which increase during the height of digestion.<sup>16</sup> These contractions usually exert but slight pressure within the viscus, although they are capable of exerting considerable pressure when the walls are thrown into a spasmodic contraction. The bile which has entered the gallbladder differs from that which comes directly from the liver.<sup>17</sup> This difference, however, is mainly, and may be wholly, due to the increased mucus content which the mucosa of the gallbladder adds to it.

The results of our own experiments and of those of other investigators<sup>4</sup> prove that usually all the ducts outside the liver dilate after the removal of the gallbladder. This is the most conclusive proof obtained to show that at least in some of certain species the gallbladder has a definite function.

We have attempted to determine the practical significance of the gallbladder by a comparative study. If the gallbladder is of any functional importance, it is reasonable to suppose that animals which do not possess the organ must have developed some means of compensation for the lack of it. This study includes the obtaining of critical data concerning the biliary tract in species of animals with, and other species without, a gallbladder, together with an attempt to compare and correlate these data, assuming that one or more points of difference might be found between the two groups of animals which would add to our knowledge concerning the function of the gallbladder. While some

comparative work has been done on these structures, it consists, for the most part, of a study of the grosser relationships. As our study involves many different investigations, only brief general deductions can be made at present. We have attempted to collate the data from a comparative standpoint and in relation to the three possible functions of the gallbladder. One of the most striking things noted in a review of our material is the marked individual variation in the anatomy of the biliary tract and, in a lesser degree, the same is true of the physiologic reactions studied. These variations make it difficult to draw conclusions (Table 1).

While we are securing data in regard to the biliary tract of all the common laboratory and domestic animals, only that will be presented which concerns comparable species, some of which do not possess a gallbladder.

Dilatation of all the extrahepatic ducts following the removal of the gallbladder does not take place if all the muscle-fibers are dissected free from the intramural portion of the duct.<sup>9</sup> From these results great importance is attached to the interrelation of the action of the gallbladder and the sphincter of Oddi. Accordingly, it was anticipated that either an anatomic or physiologic difference would be found in regard to the sphincter in animals with a gallbladder as compared with those which do not possess one. The sphincter of Oddi has been studied anatomically by Oddi<sup>15</sup> and by Hendrickson.<sup>5</sup> Archibald<sup>1</sup> seems to have been the only investigator of its physiologic action. Species which do not possess a gallbladder were not included in the series studied by these investigators.

#### DATA ON EXPERIMENTS

The material for the anatomic study of the sphincter was secured immediately after death and fixed in formalin. The specimen was trimmed to the smallest size which would give the complete course of the duct, and paraffin serial sections were made.

A histologic study of the sphincter was made in the following species of animals which have a gallbladder: Guinea-pig, rabbit, cat, dog, goat, ox, and striped gopher (*C. tridecemlineatus*). A comparative study of the sphincter in the deer, horse, pocket gopher (*G. bursarius*), and rat, species which do not possess a gallbladder, was also made.

In each species the bile-duct was found to be surrounded by definite bundles of smooth muscle, contraction of which closed the lumen of the duct. The amount of muscle tissue and the arrangement of it differed slightly in the various species, depending probably on the difference in the thickness of the wall of the duodenum and on the course of the duct.

TABLE 1.—VARIATION IN THE DIMENSIONS OF THE DIFFERENT COMPONENT PARTS OF THE BILIARY TRACT IN DIFFERENT SPECIES AND PERSONS

## A. SHOWING THE AVERAGE OF THE DIMENSIONS IN VARIOUS SPECIES

	WEIGHT	DIAMETER COMMON DUCT	LENGTH COMMON DUCT	DIAMETER CYSTIC DUCT	LENGTH CYSTIC DUCT	CAPACITY GALL-BLADDER	DISTANCE PYLORUS TO OPENING OF COMMON DUCT
Dogs—Average weight and measurement of 29 animals.....	kg. 8	mm. 2.9	mm. 57.6	mm. 2.2	mm. 18.6	c.c. 16.6	mm. 38.0
Monkeys—Average weight and measurement of 14 animals.....	gm. 1722	3.0	23.5	2.2	12.2	2.3	20.0
Rabbits—Average weight and measurement of 30 animals.....	gm. 1752	2.2	35.0	1.4	18.7	1.6	7.3
Guinea-pigs—Average weight and measurement of 16 animals.....	gm. 437	1.8	12.6	1.1	11.2	0.8	5.6

## B. INDIVIDUAL WEIGHT AND MEASUREMENT OF FIVE ANIMALS OF EACH SPECIES SELECTED FROM THE PRECEDING SUBDIVISION "A" BECAUSE THEY APPROXIMATE A UNIFORM SIZE IN EACH GROUP

	SEX	CONDITION	WEIGHT	DIAMETER COMMON DUCT	LENGTH COMMON DUCT	DIAMETER CYSTIC DUCT	LENGTH CYSTIC DUCT	CAPACITY GALL-BLADDER	PYLORUS TO OPENING COMMON DUCT	WEIGHT OF LIVER
Dogs.....	M	Thin	kg. 14.0	mm. 3.0	mm. 57.0	mm. 2.5	mm. 27.0	c.c. 20.0	gm. 43	gm. 420.0
	M	Thin	13.2	2.5	70.0	2.0	22.0	17.0	55	440.0
	F	Good	9.8	3.0	57.0	2.5	15.0	9.0	42	340.0
	F	Good	9.1	3.0	60.0	2.0	17.0	14.0	45	470.0
	M	Good	8.1	2.5	65.0	2.0	11.0	12.0	40	350.0
Average.....			10.8	2.8	61.8	2.2	18.4	14.4	45	404.0
Monkeys.....	F	Thin	gm. 2050	3.5	26.0	3.0	18.0	0.2	20	95.0
	F	Thin	2040	3.0	37.0	2.5	14.0	2.6	25	80.0
	F	Thin	1890	3.0	16.0	3.0	11.0	1.5	21	80.0
	F	Thin	1650	3.0	35.0	2.0	12.0	3.0	10	70.0
	F	Thin	1575	3.0	28.0	2.0	8.0	4.0	24	50.0
Average.....			1841	3.1	28.4	2.5	12.6	2.6	20	71.0
Rabbits.....	M	Good	gm. 2385	2.5	37.0	1.5	25.0	3.6	8	83.0
	F	Good	2335	2.0	47.0	1.5	21.0	2.2	10	85.0
	F	Good	2280	2.5	40.0	2.0	16.0	3.2	6	105.0
	M	Good	2275	2.0	40.0	1.5	12.0	2.0	8	60.0
	M	Good	2150	2.5	45.0	2.0	24.0	2.5	6	110.0
Average.....			2705	2.3	41.8	1.7	19.6	2.7	8	88.6
Guinea-pigs.....	M	Good	gm. 775.0	2.5	15.0	1.5	12.0	1.2	8	44.0
	M	Good	755.0	2.0	20.0	1.0	11.0	1.0	6	33.0
	M	Good	707.0	2.0	20.0	1.5	10.0	0.8	6	32.0
	M	Good	652.0	2.0	18.0	1.0	10.0	1.2	5	32.0
	M	Good	560.0	2.0	12.0	1.5	12.0	0.8	5	40.0
Average.....			689.8	2.1	17.0	1.3	11.0	1.0	6	36.2



However, no constant difference was observed in the histology of the sphincter in animals with a gallbladder as compared to those not having this organ. It was not possible to make any specific anatomic differentiation in the sphincter of Oddi in the two groups of animals.

The physiologic data consist of the estimation of the tone of the sphincter in anesthetized animals. The animal was lightly etherized and a cannula was placed in the common bile-duct, with its point directed toward the duodenum. To this cannula was attached an upright glass tube having an internal diameter of about 2.5 mm. and being about 30 cm. in length. An aqueous eosin solution, having a specific gravity but slightly greater than distilled water, was allowed to run slowly into this tube until the pressure was great enough to force some of the solution into the duodenum. The length of the column of water after the fluid became stationary, expressed in millimeters, was taken as a measure of the tone of the sphincter.

It is obvious that this is not absolutely the correct measure of the tone of the sphincter, as other factors, such as friction, especially in animals possessing a very small duct, and anesthesia, etc., complicate the results. However, control experiments, in which the tone of the sphincter was decreased or abolished by deep etherization, bleeding or formalin injections, proved that this method was fairly correct.

The pressure withstood by the sphincter was measured in the following species of animals which have gallbladders, namely: the cat, dog, goat, rabbit, guinea-pig, and striped gopher.

The pressure was found to vary considerably in the different species and the different animals, making it difficult to draw conclusions. However, the data show that, under light ether anesthesia, the tone of the sphincter in each species of animal possessing a gallbladder which was tested, except the guinea-pig, would withstand a pressure of 100 mm. of water. Sometimes the pressure withstood was much greater, and very rarely slightly less than 100 mm.

In the guinea-pig the pressure withstood was rarely over 75 mm., and frequently considerably lower. This was partially due to the trauma incident to the technical difficulties encountered in inserting the cannula.

The pocket gopher and rat were the only species obtainable without a gallbladder which were suitable for the investigation of the tone of the sphincter. The results of a large number of experiments are the same: in no instance was any pressure or, at most, only very slight pressure, usually not over 30 mm., maintained by the sphincter. In most cases

all the fluid passed into the duodenum. This would seem to show that the sphincter is not physiologically active in species of animals without a gallbladder, or, at least, not active to the same degree as in species possessing a gallbladder.

The anatomic variation in the dimensions of the common bile-duct has been considered as a possible means whereby an animal without a gallbladder compensates for the lack of it. Data have been obtained in regard to both the diameter and length of the common duct in animals with and without a gallbladder. The data secured, which are not yet completed, are quite variable, and it is obvious that it is difficult to make comparisons. However, after considering the variations both as regards the animal and the species, the results do not seem to warrant the belief that there is any relation between the dimensions of the common duct and the presence or absence of the gallbladder. The comparison of a few species of animals illustrates this particular point. The horse, which does not possess a gallbladder, has a relatively short duct with a large diameter, while the ox, which possesses a gallbladder, has a duct of very nearly the same dimensions. The same is true in comparing the deer and goat. However, the rat and pocket gopher, both being species without a gallbladder, have both comparatively and usually actually longer ducts, with a narrower lumen, as compared with such species as the guinea-pig, rabbit, and striped gopher, all of which possess a gallbladder (Table 2).

TABLE 2.—THE COMPARATIVE LENGTH AND DIAMETER OF THE COMMON DUCT IN ADULTS OF SPECIES WITH A GALLBLADDER (RABBIT AND GUINEA-PIG) AND SPECIES WITHOUT A GALLBLADDER (HORSE, RAT, POCKET GOPHER)

Note that the dimensions of the common duct vary in different species, regardless of whether a gallbladder is present or not.

SPECIES	LENGTH OF COMMON DUCT	DIAMETER OF COMMON DUCT	DISTANCE OF PYLORUS TO POINT OF ENTRANCE OF COMMON DUCT INTO DUODENUM
Ox.....	4-7 cm.	7-8 mm.	50-70 cm.
Rabbit.....	2-5 cm.	1.5-3.5 mm.	0.5-1.5 cm.
Guinea-pig.....	1-2 cm.	1.5-2.5 mm.	0.4-0.8 cm.
Horse.....	4-6 cm.	10-20 mm.	10-20 cm.
Rat.....	2-3 cm.	0.6-1.0 mm.	1.5-2.5 cm.
Pocket gopher.....	6-7 cm.	0.6-1.0 mm.	4-5 cm.

A comparison of the thickness of the walls of the common bile-duct in the species of animals compared herein does, however, reveal a dif-

ference. In general, the walls of the ducts in species of animals which do not possess a gallbladder are thicker and contain more muscle than the duct walls of those species having a gallbladder.

One of the points at which the biliary tract differs greatly in various species is the distance from the pylorus at which the common bile-duct enters the duodenum. As there might be a relationship between bile escape and acid escape into the intestine with regard to alkali control in the duodenum, some comparative data upon this point were obtained. However, no differentiation between groups of animals having a gallbladder and those without one can be made in this regard. Examples are cited as follows: The common duct of the horse, which does not have a gallbladder, enters the duodenum between 10 to 20 cm. from the pylorus, while that of the ox, which has a gallbladder, enters between 50 and 70 cm. from the pylorus. On the other hand, the duct enters the duodenum about 0.5 to 1.5 cm. from the pylorus in the rabbit and 0.4 to 0.8 cm., in the guinea-pig, both of which have a gallbladder, and 1.5 to 2.5 cm. in the rat and 4 to 5 cm. in the pocket gopher, both species which do not possess a gallbladder (Table 2).

The same is true in regard to the relationship of the pancreatic duct to the common bile-duct. This relationship varies greatly in the different species of animals, but there is no constant difference in this respect in species possessing a gallbladder as compared with those without one.

The secretory pressure of the liver has been investigated by several observers,<sup>6, 14</sup> but it appears never to have been measured in species of animals without a gallbladder. The method employed by us consisted in placing a cannula in the common duct of an etherized animal; an upright glass tube was then attached to this cannula and the lower end of the tube was placed in approximately the same plane as that which passed through the center of the liver. The height to which the bile rose in this tube, expressed in millimeters, was taken as the secretory pressure of the liver. Our results show that there is no difference in the secretory pressure of the liver in animals with a gallbladder from that of those without one (Table 3). Any one who has measured the pressure in the common bile-duct appreciates the great influence of respiration on intra-duct pressure. This has formed the basis for one of the recent theories of the function of the gallbladder.<sup>19</sup> A comparison of animals using the diaphragm to a great extent, however, does not reveal a difference such as to show whether or not they have a gallbladder. It is

impossible to compare the horse and deer with the rat and pocket gopher in regard to their life activities, excepting by contrast. On the other hand, several species, as the dog and rabbit, compare quite closely to the horse and deer so far as the need for a powerful diaphragm is concerned.

TABLE 3.—THE MAXIMUM SECRETORY PRESSURE OF THE LIVER IN THREE SPECIES OF ANIMALS, ONE OF WHICH DOES NOT POSSESS A GALLBLADDER (RAT)

NUMBER	RABBIT		GUINEA-PIG		RAT	
	Weight	Secretory Pressure	Weight	Secretory Pressure	Weight	Secretory Pressure
1.....	2000	308.0	775.0	200.0	190	225
2.....	2275	245.0	707.0	210.0	160	200
3.....	2155	250.0	755.0	218.0	180	215
4.....	1765	240.0	480.0	190.0	190	225
5.....	2440	225.0	540.0	195.0	165	230
	2127	253.6	651.5	202.6	177	219

Many observers have stated that the gallbladder could not functionate as a reservoir. W. J. Mayo<sup>12</sup> gives two reasons for this—first, that the relative capacity of the gallbladder to the amount of bile secreted is too small, being about 1 to 40 or 50 in man; and, second, the propulsive power of the gallbladder is not sufficient to empty it quickly. We obtained some comparative data on this point by measuring the rate of bile flow for about two hours in different species, after obtaining the capacity in relation to the rate of flow.

The method consisted in etherizing an animal, placing a cannula in the common duct, and measuring the amount of bile secreted for a definite length of time. After the collection of bile was taken the gallbladder was removed and its capacity, when it was completely filled, not distended, was measured. Naturally, the rate of bile flow was complicated by the anesthetic, as was shown by the fact that usually the amount of bile collected during the first half-hour period was the greater, but this was the only practical method to employ in small animals like the guinea-pig, the rat, etc., and the results, while individual variations are very great, are certainly comparable. The readings, however, are probably much too low in each instance.

In general, our results show that in each species of animals tested the

gallbladder could hold less than the amount of bile secreted in one-half hour, even when the animal is etherized (Table 4).

TABLE 4.—THE RELATIONSHIP BETWEEN THE RATE OF BILE-FLOW AND THE CAPACITY OF THE GALLBLADDER IN TWO SPECIES

The collections of bile were made while the animal was under an anesthetic and the rate of bile secretion probably much decreased. Even under these conditions the gallbladder never had a capacity for more than 2 per cent of the amount of bile secreted in twenty-four hours.

ANIMAL	WEIGHT	LENGTH OF TIME BILE WAS COLLECTED	AMOUNT OF BILE COLLECTED	ESTIMATED AMOUNT OF BILE SECRETED IN TWENTY-FOUR HOURS	CAPACITY OF GALLBLADDER	PERCENTAGE OF BILE SECRETED IN TWENTY-FOUR HOURS WHICH THE GALLBLADDER WILL HOLD	WEIGHT OF LIVER
Rabbit.....	2440.0	2 hrs.	10.0	120.0	2.40	2.0	75.00
Rabbit.....	2275.0	2 hrs.	12.8	153.6	2.00	2.0	75.00
Rabbit.....	2155.0	2 hrs.	16.6	199.2	2.00	1.0	95.00
Rabbit.....	1765.0	2 hrs.	9.0	108.0	1.40	1.3	65.00
Average.....	2158.8	..	..	122.7	1.95	1.4	71.25
Guinea-pig..	707.0	2 hrs.	5.0	60.0	0.80	1.3	32.00
Guinea-pig..	560.0	2 hrs.	6.5	78.0	0.80	1.0	40.00
Guinea-pig..	652.0	2 hrs.	8.5	102.0	1.20	1.0	32.00
Guinea-pig..	390.0	2 hrs.	4.4	52.8	0.60	1.1	20.00
Average.....	561.8	..	..	73.2	0.85	1.1	31.00

The bile which has entered the gallbladder normally has a much higher content of solids than the bile which comes directly from the liver. This is shown by a comparison of the specific gravity of the two fluids. In the few instances in which this has been done, the specific gravity of the bile contained in the gallbladder was much greater than that of the bile collected directly from the liver.

Another structure in the biliary tract, the function of which is unknown, is the system of folds of mucosa called the valves of Heister.<sup>1</sup> Logically they would be considered as mechanically adapted to prevent the bile from entering the gallbladder. We have measured the resistance which they offer and found that it never exceeded 30 mm. of water in the individual animals studied.

It should be emphasized that the gallbladder, in so far as it is possible to determine, is not essential to the maintenance of health. Human beings have lived for many years in perfect health after its removal.<sup>10</sup> One of our dogs lived for three and a half years after removal of the gallbladder and was always in excellent condition. We cannot say whether or not there are changes in the gastric and pancreatic secretions, as Rost

asserts, because our experiments up to the present time on this point are too few from which to draw conclusions. The results of our comparative studies which, it must be emphasized, have not yet been completed, allow the following tentative statement to be made:

#### NEGATIVE FINDINGS

1. There is no specific demonstrable difference in the anatomy of the sphincter of Oddi in species of animals with a gallbladder as compared to those without one.

2. The dimensions of the biliary tract are no different in species of animals without a gallbladder, when considered as a group, from those species possessing a gallbladder.

3. No differentiation between groups of animals having a gallbladder and those without one can be made in regard to—(a) the relationship of the pylorus to the point of entrance of the common bile-duct and (b) the relationship of the pancreatic duct to the common bile-duct.

4. There is no special difference in the secretory pressure of the liver in species of animals with a gallbladder as compared to those without one.

#### POSITIVE FINDINGS

While the following statements are substantiated by the data obtained, it is emphasized that the species of animals without a gallbladder studied so far are few.

1. The sphincter of Oddi appears to be more or less physiologically inactive in species of animals without a gallbladder.

2. The walls of the common bile-duct seem to be relatively thicker in species of animals without a gallbladder as compared to those possessing this organ.

The results of these studies show that there are some facts which support two of the major theories concerning the function of the gallbladder. A consideration of the full functional significance of the gallbladder must include the recognition that (a) it does add something to the bile, and (b) it does influence the flow of bile.

Probably in no species of animal is the gallbladder capable of holding more than 5 per cent of the total amount of bile secreted in twenty-four hours, and in most cases it may contain little more than 1 per cent. It is, therefore, impossible for the gallbladder to functionate as a true reservoir in the same sense that the urinary bladder does.

There is no doubt that the mucosa of the gallbladder adds something

to the bile. The character of the secretion and its functional significance has been contradicted by other investigators, and our own data are too few at present to draw conclusions. It may be that this secretion aids the action of bile or has other functions, but the only definitely known addition the gallbladder makes to the bile is mucus.

The functional significance of the gallbladder seems to be intimately connected with the fact that it is mechanically adapted to change the escape of bile into the intestine from a more or less continuous flow into an intermittent one. Studies on animals, practically always dogs, with biliary fistula, show that the liver secretes bile continuously, although the rate varies considerably. In most instances, however, in which duodenal fistulas have been formed, the escape of bile into the intestine has been intermittent. No studies seem to have been made on animals without a gallbladder in regard to the flow of bile into the intestine, but it seems that, in all probability, it would be continuous with liver secretion. We have observed this in the rat and pocket gopher, but the experiments were complicated by the necessary anesthetic. Under such experimental conditions, the entrance of bile into the intestine in these two species was continuous, except for the slight changes produced by respiration. The fact that the sphincter seems to be inactive in species without a gallbladder would imply that this was quite the normal condition. A study of some species of animals without a gallbladder, in which it is possible to make a permanent duodenal fistula, will be necessary definitely to prove this point.

The action of the gallbladder seems to be as follows: The liver secretes bile more or less continuously. Under normal conditions this is secreted under very low pressure. The sphincter at the opening of the common bile-duct is normally under tone which is great enough to increase the intra-duct pressure above the resistance offered to the entrance of bile into the gallbladder. At intervals the sphincter relaxes, allowing bile to flow into the intestine. The mechanism controlling the action of the sphincter is not understood, but is known to be under nervous control.<sup>13</sup> The gallbladder not only acts as an expansile chamber for the accommodation of the difference in rate of bile secretion and bile discharge, but it also prevents some of the fluctuations in intra-duct pressure which would occur during respiration in all instances in which the duodenal sphincter is active. It should be appreciated that in all species in which the sphincter is constantly active some mechanism like the gallbladder is necessary.

A description of the action of the gallbladder does not explain its function. Why it should be desirable in some species of animals to allow the bile to enter the duodenum at the same rate as the liver secretion, and in other species, closely related and having practically the same physiologic environment, to have developed a mechanism whereby it pours intermittently into the intestine, is not clear. More investigation will be necessary to eliminate this question. These future researches should include—(1) a study of the sphincter in larger series of animals without a gallbladder and (2) a determination of the mechanism controlling the sphincter in species of animals with a gallbladder.

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## SURGERY OF THE GALLBLADDER AND THE BILIARY DUCTS\*

E. S. JUDD

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Infection and malignancy are conditions which enter into the etiology of surgical lesions of the biliary tract. The contention that infection enters this region much more often by way of the general circulation than was formerly believed is supported by the results of experimental work on animals and also by the fact that infections in this tract are, in many instances, only a part of a more general infection, as is frequently shown by the presence of lesions existing in the appendix, duodenum, or stomach at the same time. Whether the infection is primary in any one of these foci and from it distributed to the other regions, or whether infection begins at the same time at several different points, owing to organisms circulating in the blood-stream, cannot be definitely decided. It is, however, of practical importance that surgical procedure for lesions of the biliary tract will usually involve exploration of these several areas, which adds little to the operation.

Undoubtedly, the entrance of the infection is sometimes through the portal circulation and the liver. In such cases infection exists within the liver as well, though apparently this is eventually relieved by the proper surgical treatment. Infection persisting in the liver may in some instances be the cause of a recurrence of symptoms at a future time. The formation of calculi, which is usually the result of invasion by some type of bacteria, apparently takes place in the gallbladder or ducts or even in the intrahepatic ducts, although as stagnation is probably an important factor in stone formation, the stones more commonly have their origin within the gallbladder.

Surgery in malignant diseases of this region is usually palliative, and consists in devising some method by which the bile may be diverted into another part of the intestinal tract. Carcinoma of the gallbladder

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s rare and is seldom discovered in time to allow a radical removal. Primary carcinoma of the common duct is at times found when it can be excised and the tissues reconstructed with some hope of a complete cure. An obstructing malignant growth at the ampulla or in the head of the pancreas is more often seen. This necessitates joining the gallbladder to the stomach or intestine.

#### CLINICAL CLASSIFICATION OF CASES

For the purpose of reviewing the clinical features in diseases of the gallbladder and its ducts they have been considered in four groups.

*Group 1.*—In this group are those cases of a more or less chronic cholecystitis producing dyspepsia and at times acting as a focus for a more or less general infection. Such cases were mentioned by Moynihan as presenting the inaugural symptoms of gallbladder disease, and were those which formerly were slow in coming to surgeons. At the present time such conditions are much better understood. The clinical history in this group is not definite, and most intensive study is necessary before treatment can be recommended. All other possible lesions, of which there are many, must be excluded. The pain is usually not at all typical and is apt to be almost constant. A slight jaundice is frequently present and is sometimes persistent; attacks with a rise of temperature may be a part of the syndrome suggesting that the infection extends beyond the gallbladder. Often the condition has symptoms of general toxemia associated with it. The clinical evidence in many instances suggests that the neuritis or general rheumatic features are produced by an infected gallbladder which is acting as a focus for the general infection. Neuritis especially seems to be a part of the syndrome in some of these cases. Many of the patients with general toxemia complain of innumerable points of tenderness and pain, and great caution should be observed in assuming that these difficulties arise from the gallbladder. On the other hand, there can be no question that the infected gallbladder sometimes is a focus for general infection, and that this infection will subside when attention has been given to the gallbladder.

In many instances cholecystitis is undoubtedly a forerunner of the formation of calculi, although, in a certain definite percentage of cases, cholecystitis remains a separate entity without showing any evidence of stone formation. Just what difference there is in the pathology and bacteriology between cholecystitis with stones and cholecystitis without stones has not been definitely determined, although inflammation

of the strawberry type may reach a very extreme degree without the formation of stone. It exists more often without stones than with them, so that apparently stones not only are the result of infection, but also are the result of certain definite types of infection, and possibly occur under specific conditions. Gangrene and perforation of the gallbladder may occur without any evidence of calculi. At the time of exploration, it may be difficult to make out the pathologic conditions in the gallbladder even when the clinical features are very definite, as the gallbladder may appear quite normal. It must be granted that there is a certain percentage of such cases in which an exploration is made on good clinical evidence and in which no definite pathologic condition can be demonstrated. While at times it may seem advisable to remove a gallbladder which appears and feels quite normal, at the same time it must be borne in mind that in order to obtain satisfactory results in any surgical procedure we must determine the basis for that procedure on the pathologic as well as on the clinical evidence, and that if an opinion is formed from the clinical picture alone, we may be led astray. It would be well to recall the very unsatisfactory results obtained in certain gastric cases some years ago when gastro-enterostomies were performed without its first being made certain that an ulcer was present. In those cases in which ulcer did exist, the results were good; but if the symptoms were being produced by some other pathologic condition, the patient was worse off than before operation.

The results of certain operations on the colon make it seem that the absolute basis of most surgical operations must lie in the pathologic lesion itself. If there is cholecystitis, the gallbladder wall is usually thickened, white, and is either not compressible or empties very slowly on pressure. The fact that the gallbladder cannot be compressed is not in itself sufficient evidence to warrant operation. At times the small white spots in the mucosa of the gallbladder may be seen through the gallbladder wall in the strawberry type of infection. A considerable enlargement of the regional lymphatics will sometimes help in making a diagnosis. These lymphatics are always greatly enlarged and softened in the presence of marked cholecystitis. In this condition, which approximately constitutes 10 per cent of all cases of cholecystitis in which the pathology is not evident on exploration, I believe that in most instances the trouble is in the gallbladder or pancreas or both, and that in a certain few the difficulty comes from a mistaken diagnosis. If all other possible lesions have been excluded and the clinical syndrome is

positive, it may be necessary, occasionally, to remove what seems to be a fairly good gallbladder. On several occasions I have made the mistake of saving a gallbladder because of a lack of pathologic evidence for removing it, only to have the patient return with the same complaint, and to find at a second operation a very definite cholecystitis. For a time in these doubtful cases it was our custom to open the gallbladder and remove a small piece of the wall for pathologic examination before doing anything more radical. This was not of enough assistance to warrant its continuation because, possibly, at the time of the exploration no histologic changes actually existed, or else the section removed was not taken from the affected quadrant of the gallbladder. Drainage of the gallbladder in such cases is not sufficient. In most instances the symptoms are relieved for a time after drainage, but there is a recurrence of symptoms in too large a number of cases, as might be expected from the nature of the trouble, so that removal of the gallbladder is indicated in all cases of cholecystitis.

*Group 2.*—In the second group of cases are included those patients having typical gall-stone colic. The symptoms are very definite in every respect. The attacks are short, sharp, and colicky, with characteristic radiation and residual soreness. There is usually no chill, fever, nor jaundice. Morphine and external heat are required to relieve the pain. Patients often have these attacks for a number of years without seeking treatment, probably because they feel perfectly well as soon as the pain subsides. On exploration, a gallbladder apparently normal in size, color, and thickness, and containing one or many stones, may be found; or, in addition to the stones, any degree of inflammation may be present in the gallbladder at the same time. It is surprising in some instances to see what a good condition will be maintained in the gallbladder in spite of a large number of irregular stones. If the cystic duct is completely blocked, hydrops is found, the old colicky pains have probably disappeared, and the evidence of a mild persistent infection remains. In this group the clinical features and pathologic conditions are definite, and removal of the gallbladder is indicated.

Recently, in reviewing a large series of all types of gallbladder cases in which recurrence of symptoms had taken place some time after operation, we found that the largest percentage of recurrences occurred in this group. The first operation in most of the cases of recurrence had been drainage of the gallbladder, and the recurring symptoms were almost always due to stones in the gallbladder which had either been over-

looked or had reformed after drainage. There was a great deal of evidence to show that stones often do reform in the gallbladder. In many of the cases of recurrence the patients had been entirely free from trouble for from three to six years after drainage, when there was a sudden return of the former attacks, and exploration showed the gallbladder again filled with stones. In most instances such gallbladders are probably functionless after the first operation. Furthermore, there is sufficient evidence at the present time to show that the patients are quite as comfortable without their gallbladders as they were with them.

*Group 3.*—In this group are placed those cases of typical cholangitis with stones in the common duct which at the time of the attack produce an obstruction to the flow of bile and a resulting jaundice. Each attack is associated with chills and fever as well as jaundice. In many such cases there are also stones in the gallbladder, which is most often contracted. There may also be stones in the cystic and hepatic ducts, and frequently there are swelling and hardening of the pancreas. In the performance of all gallbladder operations it is essential that the ducts shall be explored as carefully as possible, because stones are found in them when least expected. Such exploration should be confined to palpation unless there is clinical evidence that warrants opening the duct for examination. In cases of typical cholangitis, the common duct should always be opened and, if possible, the exploration should be done with the finger in the duct, to make sure that all the stones have been removed from the hepatic ducts and from the ampulla. It is usually best in these cases to remove the gallbladder after the common duct has been cleared and the drainage placed. Stricture apparently does not follow ordinary uncomplicated operations of the common duct. It has been our custom to drain the common duct with a rubber tube, stitching the opening in the duct accurately about the tube. The gallbladder in these cases is frequently destroyed or nearly so, and a more complete recovery will follow its removal. If there are complications or if there is any question about the patency of the common duct, the gallbladder should be saved.

*Group 4.*—In Group 4 are the atypical cholangitis cases with painless or almost painless jaundice. I think it is quite impossible to make a definite diagnosis before exploration in a large percentage of these cases, and, in view of the fact that there is so much uncertainty about the diagnosis, in all cases of painless jaundice in which a positive clinical diagnosis cannot be made, the patient should be subjected to an exploration.

The symptoms may be produced by biliary cirrhosis or by malignant disease at the ampulla or at the head of the pancreas, and sometimes this form of jaundice may be produced by an inflammation in the head of the pancreas, although this occurrence is probably quite rare. Any variation in the jaundice or suggestion of fever or chills should be an indication for exploration. We have seen a considerable number of persons with jaundice in whom the symptoms were being produced by stone in the common duct and who insisted that they had had no pain at any time. Cases in this group are not ones in which it is especially attractive to operate, as the operation may be very difficult and the patient in none too good a condition. However, the greatest difficulty usually arises from oozing and hemorrhage, which may come from the wound or possibly from the mucous membrane of the nose, throat, or intestinal tract, and may begin at any time up to eight or ten days after the operation. This oozing results from the condition of the blood, a careful study of which before operation is often very helpful. As a general rule, if the coagulation time is more than from twelve to fifteen minutes, the risk from any operative procedure will be very great. However, it has been noted in some cases in which there was a very long coagulation time that there was no tendency to ooze, while in others in which the coagulation time was well within normal limits there was considerable difficulty from oozing. In operating on these patients, jaundice should always be considered an indication of added risk, and if it is subsiding, the operation should be postponed. The use of calcium salts before or after operation has not been of distinct advantage in our experience with these cases. Too much emphasis cannot be laid on the advisability of transfusing all patients with jaundice before operation. To accomplish the most good, transfusions must be made before any oozing begins.

If, in spite of this procedure, oozing does start from the wound and from the mucous membranes, as it may at about the end of the first week after the operation, aspiration of the congested liver with a large trocar or even opening well into the liver substance is of great benefit. I have found this to be true in the few cases in which I have tried it. The bleeding from the wound in the liver is very profuse, and this is probably the way in which the benefit is derived. If the bile flowing from the tube in the common duct stops or is greatly reduced, it is almost certain to mean that oozing will take place, while, on the other hand, if bile drainage continues, there is not this danger of oozing, so that oozing depends directly on the capacity of the liver cells to functionate.

In these cases, naturally, the liver cells are greatly congested and swollen so that they cannot secrete unless this pressure and swelling are relieved which we have accomplished in these few cases by means of drainage through incisions into the liver. Frequently the bile has started to flow very soon after this procedure. The common duct drainage-tube should be left in place a long time. Frequent irrigations of physiologic sodium chlorid solution seem to bring away considerable clotted blood and, to a certain extent, relieve congestion. The most desperate cases are those in which the obstruction of the common duct is due to a stricture or in which the duct had formerly been ligated or divided during an operation. Such cases are becoming very common since the more frequent performance of cholecystectomy. The jaundice is generally complete, and no bile passes into the intestinal tract. The liver has usually been entirely closed off for from several months to a year or more, and the difficulty lies in establishing liver function after the duct has been reconstructed. The jaundice often persists in spite of bile drainage, and almost any type of toxemia may appear. Transfusion and aspiration of the large congested liver may be very useful.

#### EXPERIMENTAL STUDY OF THE REMOVAL OF THE GALLBLADDER

A few years ago Dr. F. C. Mann and I removed the gallbladders from various species of animals and studied the effect of such procedure on the remaining portion of the biliary tract. \* \* \* \* (See pp. 96-105.)

#### TECHNIC OF THE REMOVAL OF THE GALLBLADDER

The technic of operations on the gallbladder and ducts is definitely established, though there is much variation in the operation according to the judgment and method of proceeding of the individual operator. There can be no question that cholecystectomy is as safe a procedure as cholecystostomy, if the operator has had ordinary experience. The immediate convalescence is more satisfactory and the ultimate results certainly are better following cholecystectomy. Whether the removal of the gallbladder be done by starting at the fundus and dissecting downward or by starting at the cystic duct and freeing it first, there are two main factors which must be emphasized: 1. The cystic artery must be

\*Judd, E. S., and Mann, F. C.: The effect of removal of the gallbladder: An experimental study. *Surg., Gynec. and Obst.*, 1917, xxiv, 437-442. Judd, E. S.: Cholecystitis: Changes produced by the removal of the gallbladder. *Boston Med. and Surg. Jour.*, 1916, clxxiv, 815-825. Mann, F. C.: The function of the gallbladder: An experimental study. *New Orleans Med. and Surg. Jour.*, 1918, lxxi, 80-92.

ied securely. I do not believe it is material whether this is tied in connection with the cystic duct or separately. If the artery can be isolated with the duct and tied at the same time, it will be sufficient. 2. In order to prevent any disturbance of the common duct, it is absolutely essential that a complete isolation of the cystic duct be made before any clamps or ligatures are applied. The most serious consequence of a cholecystectomy is trauma to the common duct. The duct has undoubtedly been caught in clamps and completely divided a great many times. This cannot possibly happen if the cystic duct is isolated beforehand. In an endeavor to remove all of the cystic duct, the common duct has often been injured or even ligated. Judging from our review of recurring cases it does not appear necessary to remove all of the cystic duct to obtain satisfactory results. In a very small percentage of cases, if at all, will the stump of the cystic duct or the entire cystic duct cause trouble after cholecystectomy.

While removal of the gallbladder should be the operation of choice in cases of cholecystitis with or without stones, still in a certain small percentage of cases it is much better to do a cholecystostomy primarily and then to remove the gallbladder in a second operation if it becomes necessary. This would seem to me to be the best plan in case of much infection outside of and about the gallbladder, or in cases in which there is a great amount of induration and edema about the ducts. If the infection is confined to the gallbladder, it is best to remove it if possible. Enlargement and hardening of the head of the pancreas are an indication for removal of the gallbladder in preference to drainage, and this would still hold good in the presence of a slight degree of jaundice if the jaundice is due to pancreatitis. Cholecystectomy, seemingly, accomplishes more in cases of pancreatitis associated with gallbladder conditions than does any other form of treatment. This is probably due to the changes produced in the excretory apparatus by the removal of the gallbladder. It does not seem to me to be advisable to open the common duct for exploration unless stones can be palpated or unless clinical features suggest that stones or infection are present in the duct. Dilatation of the common duct is not an indication for draining it, as this change would have taken place if the gallbladder had been out of commission for any length of time. If jaundice exists at the time of the operation, the duct, as a rule, should be opened even if no stones are palpated, as the convalescence will be more satisfactory if the infected ducts are drained. If the stones in the ampulla can be removed through an open-



ing in the duct, it is much safer and is preferable to the transduodenal operation. Exploration of the gallbladder and ducts should be performed in almost all cases of chronic jaundice in which the diagnosis is uncertain. Some of these will prove to be due to infection which can be promptly relieved; and if a malignant obstruction does exist, a palliative operation can often be done which will be very satisfactory.

# THE RECURRENCE OF SYMPTOMS FOLLOWING OPERATIONS ON THE BILIARY TRACT\*

E. S. JUDD

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The prolonged and detailed discussion regarding the advisability of drainage or of removal of the gallbladder has been valuable and convincing in that it has created a better understanding of the treatment of gallbladder conditions. Most of us are convinced that in the majority of cases the results will be more satisfactory if the gallbladder is removed, though I think we are also convinced that the organ has definite functions and should not be deliberately sacrificed unless there is sufficient evidence to show that it is a source of infection.

The function of the gallbladder is not definitely known, though probably definite compensatory changes do take place when it is removed. We have reported the results of our studies of the changes that take place when the gallbladder is removed from animals.<sup>3,4</sup> There was no dilatation of any part of the duct if the sphincter at the ampulla was destroyed at the same time that the gallbladder was removed. Removal of the gallbladder in dogs—and this probably holds true for all animals and species of animals having a functioning sphincter of Oddi—produces a uniform dilatation of all the extrahepatic biliary ducts. Investigators of the subject agree that this dilatation takes place very quickly after the cholecystectomy and soon reaches its maximum development.

The process producing the dilatation probably is as follows: The liver secretes bile almost continuously, although the rate of secretion varies. The maximum intraduct pressure at which the liver can secrete is relatively low, and probably never exceeds 300 mm. of water. The escape of bile into the duodenum is at least partially under the control of the sphincter of Oddi. This sphincter when below normal in tone may be able always to withstand the pressure of 100 mm. of water and when thrown into spasm it can resist a much greater pressure, probably as

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high as 600 mm. of water. It is also evident that, owing to the course of the common duct through the duodenal wall, passing waves of peristalsis will momentarily prevent the escape of bile into the intestine. This fluctuation of intraduct pressure produced by the variation of the rate of bile secretion and bile escape into the intestine is, in all probability, compensated by the gallbladder. After the removal of the gallbladder this mechanical action producing change in the intraduct pressure still persists, but, owing to the decrease in the total capacity of the biliary tract, the maximum pressure produced is much higher; consequently that portion of the biliary tract most susceptible to dilatation, that is, the extrahepatic ducts, dilates. The amount of dilatation will depend on—(1) the resistance to the escape of the bile; (2) the relative capacity of the biliary tract, and (3) the resistance of the duct walls or periduct structures. The secretory pressure of the liver, although varying greatly, will always be enough to produce some dilatation of the ducts if enough resistance is offered to the escape of bile. In cases in which the resistance to the escape of bile is low, as occurs normally in some persons because of the lack of function of the sphincter, or, experimentally, when all the muscle-fibers surrounding the duct at its entrance into the duodenum have been destroyed, little or no dilatation will occur. Also, the duct will not dilate in those cases in which the capacity of the biliary tract is such that it can accommodate itself to the changes due to variation between the rate of secretion and the rate of escape. The pressure producing the dilatation is relatively quite low, probably seldom greater than 100 mm. of water, consequently, if the duct walls are resistant, or if other structures, such as the pancreas or adhesions, press on them, dilatation will not occur. In the dog, the weakest portion of the wall of the duct is at the juncture of the upper hepatic ducts. This region always shows the greatest dilatation after the removal of the gallbladder. These results may be controlled by ligation of the common bile-duct. In a very few hours after ligation this particular part of the biliary tract will be dilated. Whether or not the cystic duct dilates after the removal of the gallbladder depends on these same factors. It will not dilate—(1) If the resistance to the escape of bile is below the resistance of its own walls to dilatation; (2) if the capacity of the biliary tract is so great that sufficient variation in pressure does not occur to overcome this resistance; (3) if adhesions have formed around it, or (4) if other less resistant portions of the biliary tract dilate to accommodate the variation of pressure. Such dilatation has often

been observed during operations on man and is especially noticeable in hydrops of the gallbladder, in which instance the gallbladder has been without function for some time and this compensatory change has taken place. It has also been observed in persons from whom the gallbladder had previously been removed.

I have been able to obtain reports from fifteen persons who have been without their gallbladders for fifteen or more years, and, so far as I can determine, they are not inconvenienced and are living normal lives. In following up these cases, it was interesting to note that one of the frequent symptoms of cholecystitis, the frequent belching of gas, persisted in several of the cases, in spite of the fact that the patients had been without their gallbladders for so long a time. Persons who have had their gallbladders removed also often note the passage of large quantities of bile from their bowels. They state that this may come between the normal passages; it usually occurs within the first year and may then disappear. Since we know that most persons are not disturbed by the removal of the gallbladder, we certainly should feel justified in removing the organ in most instances in which we believe that the immediate and ultimate results will be satisfactory. Some investigators are inclined to believe that cholecystitis without stones and cholecystitis with stones are two entirely distinct conditions, and that cholecystitis exists continuously without the formation of gall-stones. This would certainly point to a definite indication for the removal of the gallbladder.

Recurrences are much more common following drainage of the gallbladder, and a definite number of such cases will require secondary operation, and while recurrences are much less frequent after its removal, there are not uncommon instances in which there was infection or stones in the ducts. Deaver reports that in 4.07 per cent of the cases in which he operated at one hospital the operations were secondary. He says that the most common cause of recurring trouble after drainage was stones in the gallbladder, and next in frequency were adhesions and stones in the common duct. Most of his patients required reoperation within a year. He had only reoperated in 4 cases following the removal of the gallbladder: in 2 for stricture of the pancreatic part of the common duct; in one for stone in the common duct, and in one for duodenal fistula. He further states that removal of the gallbladder reduces the risk of future trouble. Eisendrath has reported 11 cases of recurrence from various causes.

According to these observers, and from a review of our own cases, we believe that recurrences of symptoms in biliary cases are most often due to—(1) the recurrence or persistence of infection; (2) reformed or overlooked calculi; and (3) chronic pancreatitis. Faulty technic in suturing the fundus of the gallbladder to the abdominal wall seemed to be responsible for the symptoms in a number of cases of recurrence. To adhesions has been attributed the recurrence of symptoms and undoubtedly they are a factor, though in the majority of our cases in which the adhesions were most dense there seemed to be some inflammatory trouble as an etiologic factor which produced the adhesions as well as the recurring symptoms. In some of the cases in which secondary operation was necessary the adhesions were very numerous and firm.

Dr. S. W. Harrington and I have recently reviewed the histories of patients operated on for recurrence in the past two years at the Mayo Clinic. There were 2027 operations, of which 219 (10.8 per cent) were secondary. A large number (80 per cent) of the operations were for the removal of the gallbladder, a procedure which has been accepted in the clinic as the operation of choice. The drainage operation has a much higher mortality, but this is not attributed to the operation itself, since it was usually performed in cases in which the least possible operating was done because of the precarious condition of the patient, or because it was almost technically impossible to remove the gallbladder at the time. It is our custom in badly infected cases, and in patients who are poor risks, to drain the gallbladder at the first operation with the idea that it may possibly have to be removed at a later date when the patient is in better condition. However, if conditions are reasonably favorable, it seems advisable to remove all infected gallbladders at the first operation. At the present time, with a larger experience in these cases, we are removing gallbladders which previously we believed should be drained.

One hundred and twenty of the 219 secondary operations were for the removal of gallbladders which had been drained previously. There was only 0.8 per cent mortality in the series, showing that the risk in the secondary operation is no greater than in the primary operation. In 4 of the 219 cases a secondary cholecystostomy was done because the general condition of the patient contraindicated any further procedure. Two of these patients died. In 109 of the 219 operations, calculi were found either in the gallbladder, the ducts, or in both. One hundred and fifty-three patients had cholecystitis, in some instances associated

with stones. Adhesions were especially noted in 148 cases, and in 41 there was a definite pancreatitis. Either a mucous or a biliary fistula was present in 37 cases. Seventeen of the 209 patients were definitely jaundiced. At the time of the first operation stones were found in 154 of the 219 cases; in the gallbladder in 140, in the ducts in 9, and in the gallbladder and ducts in 5. Stones were found at the second operation in 109 cases; in 59 cases in the gallbladder; in 9 in the gallbladder and ducts; and in 41 in the ducts.

In 64 of the 219 cases both the primary and secondary operations were performed in our clinic, so that we had accurate data, but in the remaining cases we were dependent for the data regarding the first operation on the history given by the patient, which in all instances was not very complete. For this reason a more detailed study has been made of the 64 cases. From 51 of the patients in this group stones were removed at the first operation, and of these stones were removed at the second operation in 35. It would seem, therefore, that in some instances, at least, all of the stones were removed at the primary operation. I removed a large stone from the common duct on three different occasions from one patient. In this case the gallbladder was removed at the first operation and the patient was entirely free from symptoms for more than a year, and also for about one year following the second operation. It is now almost a year since the third operation was performed and there has been no evidence of trouble. It is often impossible to be certain that small stones have not slipped back into the liver, especially if the ducts are greatly dilated. When possible, the finger should be introduced into the lumen of the duct. On several occasions we have been able to wash out multiple small stones with the suction syringe. Long-continued drainage with the T-tube should be instituted in some of the cases. In a considerable number of the 35 cases in which stones were removed at the second operation drainage only was done and no attempt made to locate stones in the ducts at the first operation because an abscess was present. For this reason these cases could be designated as those of overlooked or reformed stones. At the first operation it seemed better to relieve the infection and then remove the stones later. Some of these cases should be classified as requiring a two-stage operation, the first for drainage of infection, usually outside the gallbladder (in one of our cases in the subphrenic space), and the second for the removal of the stone and drainage of the common duct.

In 37 of the series of 64 secondary operations a drainage operation

had been performed primarily: 29 for stones and 8 for cholecystitis. Of the 29 patients with stones in the gallbladder at the first operation, 13 had stones in the gallbladder at the second operation, and 4 of these had stones in the ducts also. It seems almost incredible that stones could have been left in the gallbladder, and in most of these cases I believe that they had either reformed in the infected gallbladder or had developed from very minute calculi buried in the mucous membrane of the organ at the time of the first operation. It is also interesting to note that of the 8 cases in which drainage was done for cholecystitis, in 2 stones or stony material which was not present at the first operation was found later. In 12 of the 64 cases the primary operation was cholecystectomy; in 6 of these stones were removed from the common duct at the second operation. Whether or not the common duct should be opened at the time of the first operation depends somewhat on the clinical history of the case. In most instances the stones can be palpated, but even if they are not felt the common duct should be opened, provided the history is suggestive, or if there is evident inflammation in the wall of the duct. I do not believe that the common duct should be probed in every gallbladder operation, since very little can be accomplished by probing a normal sized and normal appearing common duct. If there is sufficient evidence of a common duct infection, the duct should be opened even though no stones are palpated. This can be done in the ordinary case with little additional risk. From the number of instances in which patients are reoperated for stones in the common duct I think we must conclude that stones will sometimes reform in the duct.

The impressions we have gained in reviewing this series of 2027 cases are:

1. Removal of the gallbladder reduces the risk of later troubles, and ordinarily is to be preferred to cholecystostomy for drainage.
2. It is not necessary to open and probe the common duct at every gallbladder operation.
3. Infection in the liver, gallbladder, or ducts is the most frequent cause of secondary trouble, and may recur many years after the primary operation.
4. The recurrence of stones is more frequent in the gallbladder than in any other part of the biliary tract. The common duct is next in point of frequency.

5. In a definite small percentage of cases stones will be overlooked in the common duct; in other cases the stones reform in the duct.

The following are abstracts of the histories of 5 cases in which more than one operation was done for the removal of stones from the common duct. There was much evidence of reformation of stones and infection in these cases. The infection apparently persisted in some cases; in others there were no symptoms of infection over a long period.

**CASE 1 (146221).**—B. R., a male, aged sixty-two years, was first operated on Nov. 26, 1915, and two soft stones one-half inch in diameter were removed from the common duct; one was impacted in the ampulla. The patient was well for a year, except that he had an occasional chill. These grew more severe, and about one year after the operation he became jaundiced. In addition to the drainage of the common duct, the gallbladder was removed at the time of the first operation. The second operation was performed Jan. 13, 1917. At this time stones containing much muddy material were found in the remnant of the cystic duct as well as in the common and hepatic ducts. There were two large stones in the ampulla of the common duct. In this case the infection and process of stone formation apparently continued in spite of the free drainage of the ducts.

**CASE 2 (129803).**—Mrs. P. K., aged sixty-five years, was first operated on May 14, 1915, and several stones were removed from the common duct. A fistulous tract between the cystic duct and duodenum and also a pancreatitis were noted. The common duct was drained and the gallbladder removed. Seven months later jaundice appeared and there was other evidence of infection in the common duct. A second operation was performed May 17, 1916, and a stone was found in the hepatic duct.

**CASE 3 (123150).**—Mrs. J. D., aged forty-one years, was first operated on Feb. 1, 1915. There was empyema of the gallbladder, and many stones were found in the common duct. A cholecystectomy was done, the stones were removed from the common duct, and the duct drained. The patient felt well until three weeks before she returned for examination (January, 1916) because of an attack typical of stones in the common duct. The second operation was performed Feb. 11, 1916, when six small stones were removed from the common duct, and several small stones were brought down with a scoop from the hepatic duct. There was some evidence of infection in the ducts and in the liver persisting after the operation. However, there were no attacks of severe pain until March, 1917, when all the evidence of common duct stone, chills, fever, and jaundice returned. The third operation was performed June, 1917. At this time many stones were found in the common and hepatic ducts; several were wedged into the ampulla. The common



duct easily admitted a finger, and a finger could also be passed into the hepatic ducts. Drainage was prolonged and the duct washed out for several weeks. The patient has remained well since the third operation.

CASE 4 (99023).—Mrs. W. M., aged fifty-nine years, was first operated on Jan. 20, 1914, and choledochotomy and cholecystectomy were done. The gallbladder was large, thick-walled, and filled with foul-smelling, thick bile. One large and a number of small stones were found in the gallbladder and small stones and pasty bile in the common duct, which was drained. The patient had absolutely no trouble until August, 1916, two years and six months after the first operation. At this time there was a typical common duct syndrome. A second operation, choledochotomy with the removal of a stone and drainage, was performed Oct. 17, 1917. The common duct was markedly dilated and contained one stone the size of a pigeon's egg.

CASE 5 (177791).—A. O. H., a male, aged fifty-six years, was operated on first Nov. 24, 1916. The gallbladder was very large, filled with foul-smelling bile, and contained considerable flocculent material. The common duct was one-half inch in diameter and contained a soft stone, together with considerable putty-like material. Following this operation the patient regained his normal health and was well for about five months, when all symptoms of the former trouble returned. A second operation was done May 11, 1917. At this time the common duct was the size of a finger and contained a soft, crumbly stone, one-half inch by one inch, which was removed from the pancreatic end of the duct.

The following are abstracts of the histories of six cases in which a cholecystectomy as a primary operation and removal of stones from the common duct as a secondary operation were done. It is probable that infection existed in the common duct in these cases at the time of the first operation, that it became active later and was the cause of the formation of the secondary stones. In some of the cases stones may have been present at the time of the first operation.

CASE 6 (78278).—Mrs. E. A. R., aged sixty-one years. The first operation, a partial cholecystectomy for empyema of the gallbladder, was performed April 23, 1913. Stones were found in the gallbladder and cystic duct. Slight attacks occurred after the operation, although the patient was comparatively well until the fall of 1916, when the attacks became severe and there was slight jaundice. A second operation was done Oct. 27, 1916, and two stones the size of hazel-nuts were removed from the common duct. The adhesions were very marked.

CASE 7 (83151).—Mrs. P., aged thirty-eight years, was first operated on April 25, 1913. The gallbladder, which was removed, was very

thick-walled and contained pus and one large stone. There was one stone in the cystic duct. There were no symptoms whatever for two and one-half years, then repeated attacks of typical colic occurred. A second operation revealed a dilated cystic duct which had also been present at the time of the first operation. One stone, one-half by one-fourth inch, was found in the hepatic duct.

CASE 8 (146675).—Mrs. M. H., aged sixty-five years, was operated on elsewhere eight months previously, and stones had been removed from the gallbladder. Eleven weeks after the operation the attacks returned. Dec. 3, 1915, a cholecystectomy was performed. The gallbladder was large and filled with tarry bile and stony material. The common duct was dilated, and the pancreas edematous. Feb. 1, 1916, a choledochotomy was done and one stone was found in the common duct.

CASE 9 (6385).—J. M., male, aged fifty-eight years, was first operated on Nov. 19, 1915, and a cholecystectomy was done. Many stones were found in the gallbladder. Pancreatitis was present. Attacks came on very soon after the operation and in a short time were very severe. A second operation, choledochotomy, was done four months later and one stone, which could not be palpated, was removed from the common duct.

CASE 10 (156077).—Mrs. C. H., aged thirty-eight years, gave a history of typical attacks accompanied by jaundice. Cholecystectomy was performed April 11, 1916. There were a large number of stones in the gallbladder. The patient was well for six months, when there was a recurrence of the attacks. A choledochotomy was done March 22, 1917. The common duct was greatly distended and contained one stone.

CASE 11 (54104).—Mrs. L. A., aged thirty-seven years. Cholecystectomy for cholecystitis and a large number of stones in the gallbladder was performed July 15, 1915. The patient was fairly well for one year, when there was a recurrence of attacks similar to those she had had before operation. Choledochotomy was done at the second operation. The common duct was slightly dilated but no stone was found. There was a small amount of calcareous material in the bile.

The following are abstracts of 13 cases in which the gallbladder was drained and stones were removed at the primary operation, and in which stones were found in the gallbladder at the secondary operation:

CASE 12 (191934).—H. B. K., a male, aged forty-four years, was examined April 19, 1917, two weeks after the onset of attacks. Six severe attacks of acute pain and tenderness in the gallbladder area without fever had occurred. There had been no chills or jaundice. He had

lost 10 pounds in two weeks. No morphin had been given. The first operation, cholecystostomy for acute empyema of the gallbladder with stones, was done April 20, 1917. The patient gained rapidly in weight and strength, but he returned later because of mucous drainage from the wound. The second operation was done May 11, 1917. There was an acute cholecystitis on a chronic condition; the gallbladder was necrotic and a single stone blocked the cystic duct.

CASE 13 (88862).—C. L., a male, aged forty-five years, was examined July 2, 1913. He gave a history of having had three severe attacks of typical gallbladder colic in the previous two weeks. The attacks were relieved by morphin. There had been no vomiting nor jaundice. The first operation, cholecystostomy, was done Aug. 4, 1913. One large stone and bile sand were found in the gallbladder. The patient returned for examination in March, 1917. After having been well for three and one-half years he had had attacks of pain, three attacks in the preceding three weeks, very similar to those from which he suffered before the operation. There was no jaundice. Morphin had been given for relief. Cholecystectomy was performed March 14, 1917. Cholecystitis with one stone in the gallbladder was found.

CASE 14 (36335).—O. P., a male, aged thirty years, was examined April 12, 1910. He gave a history of having had in one year eight similar attacks of pain in the epigastrium radiating to the right side, to the back and shoulder. There had been no fever, vomiting, nor jaundice. Cholecystostomy was done May 10, 1910, many stones being removed from the gallbladder. The patient returned, having had more or less constant trouble beginning about one year after the operation. There had been pain in the right hypochondrium, regurgitation and eructation of gas and food; the attacks lasted from two to three hours on from two to four days. The second operation, cholecystectomy, was done April 27, 1917. Subacute cholecystitis with one stone in the gallbladder was found.

CASE 15 (5704).—Mrs. J. E. S., aged forty-one years, was examined Jan. 17, 1908. Her trouble began twenty-one years previously with indigestion, eructation of gas and food, and dull pain in the epigastrium. She was well between the attacks. Recently she had had attacks of epigastric pain, more frequent and severe, requiring morphin. There was soreness but no jaundice. A cholecystostomy for stones in the gallbladder was done Jan. 27, 1908. The patient remained well for seven years and then began to have attacks of gastric disturbance with some pain along the right costal margin. She was well between attacks. A second operation, cholecystectomy for cholecystitis with stones in the gallbladder, was done May 19, 1917.

CASE 16 (21761).—Mrs. F. J., aged twenty-five years, was examined June 3, 1909. Two months after the birth of her second child she began to have attacks of severe pain in the epigastrium, radiating to the back

and to the right shoulder. Morphin was given. Cholecystostomy was done June 24, 1909. A large number of small stones were found in the gallbladder. The patient remained well for seven and one-half years; she then had an attack of sudden severe pain in the right upper abdomen with residual soreness and digestive disturbances. Physical examination revealed a mass in the right hypochondrium. Second operation May 30, 1917. Cholecystectomy for cholecystitis with stones. The large cystic duct contained a stone; the common duct was markedly dilated.

CASE 17 (27601).—Mrs. A. M. W., aged thirty years, was examined Aug. 12, 1909. Since the patient was twelve years of age she had had innumerable attacks of epigastric pain, radiating to the back and accompanied by vomiting. The appendix had been removed five years previously but without relief. First operation Aug. 18, 1909. Cholecystostomy for stones in the gallbladder. A large single kidney was found. The patient remained well for five years. In the last three years she had had nine violent attacks (typical gallbladder colic), requiring morphin. There had been no digestive disturbances between attacks. A second operation, cholecystectomy, was done July 12, 1917. Cholecystitis, a large gallbladder filled with stones, and pancreatitis 1 on a scale of 4, were found.

CASE 18 (59889).—Mrs. H. W. C., aged thirty-one years, was examined Oct. 10, 1911. Eructation of gas and food without pain had begun ten years previously. Such digestive disturbances continued for two years. Five years previously a sudden, severe gallbladder colic occurred. There was no jaundice. Four similar attacks have occurred since then. Cholecystostomy was done October, 1911, for stones in the gallbladder. The patient returned Dec. 20, 1916. She had had no symptoms for about two years following the operation, then began having digestive disturbances, eructations of gas and food immediately after meals, and pain in the region of the right shoulder. There had been no epigastric pain, no severe colics nor jaundice. Second operation June 20, 1917. Cholecystectomy was done for stones in the gallbladder. Tuberculosis of the gallbladder and immediate vicinity was found, apparently originating near the fundus of the gallbladder.

CASE 19 (83110).—Mrs. R. C., aged fifty-seven years, was examined April 21, 1913. The patient gave a four-year history of attacks of gallbladder colics, gradually becoming more severe and frequent, and requiring morphin for relief. There had been nausea, vomiting, and residual soreness, and gall-stones had been passed on three occasions. A cholecystostomy was done April 23, 1913. A large number of stones were found in the gallbladder. The patient had no trouble for three years; she then began to have attacks of pain across the upper abdomen,

especially on the right side, the pain gradually becoming more severe with each attack. Morphine was given for relief. The attacks lasted from one to three hours. There was no vomiting or jaundice. The second operation, cholecystectomy, was done July 25, 1917. A large number of stones were found in the gallbladder and cystic duct.

CASE 20 (8302).—Mrs. F. W. K., aged twenty-eight years, was examined March 27, 1908. This patient had had typhoid fever when fourteen years of age and again when nineteen, and scarlet fever at the age of twelve. In the fourth month of her second pregnancy she had an attack of severe pain in the epigastrium, requiring morphine, but there was no vomiting, no jaundice nor soreness following the attack. Since then she had had typical attacks every three or four months, each one becoming more severe and always relieved by morphine or induced vomiting. Thirty pounds loss of weight in the preceding six weeks. The first operation, cholecystostomy, was done March 29, 1908. Stones were found in the gallbladder. The patient remained well for seven years and then, in the fifth month of her third pregnancy, she had a severe colicky pain in the right hypochondrium, radiating along the right costal margin to the right shoulder. She vomited and there was a questionable jaundice. Three similar attacks occurred before the child was born. During the intervals between attacks her digestion was good. Second operation, cholecystectomy, Feb. 3, 1916. A large number of small stones were found in a strawberry gallbladder.

CASE 21 (92462).—Mrs. M. D., aged thirty-three years, was examined Sept. 22, 1913. She gave a three-year history of attacks of dull pain under the right costal margin and eructations of gas and food. During the intervals between attacks she was entirely free from any disturbance. During the preceding year the attacks had been quite severe. The first operation, cholecystostomy, was done Sept. 30, 1913. One stone was found in the gallbladder. Three months after the operation the patient had a sudden attack of severe pain along the right costal margin radiating to the back. There was no vomiting, no jaundice, but some residual soreness. Two and one-half years after the operation the attacks became noticeably more severe, and cholecystectomy was done April 20, 1916. Cholecystitis with many stones in the gallbladder was found.

CASE 22 (28466).—Mrs. H. F. D., aged thirty-five years, was examined Sept. 1, 1909. There was a history of typical attacks of pain for six or seven years. The pain was severe, epigastric, and radiated to the back and right shoulder. A hypodermic injection was usually given. She had had three or four attacks a year, generally with vomiting. There was no mention of jaundice, fever, or chills. Cholecys-

tostomy was done Sept. 17, 1909. Numerous stones were found in the gallbladder. She returned in May, 1916, having been well for four years, but during the past three years had had several attacks of severe upper abdominal pain with bloating and soreness. Morphin had been given to ease the pain. One week previous to her return she had had terrific pain in the epigastrium, radiating to the back and right shoulder, with vomiting, chills, and fever. There had been continual aching and severe pain since that time and she gradually became more jaundiced; the temperature for three days was up to 103°. There was swelling over the area of the wound. An ice pack was applied and no food was allowed for three days. The second operation, a cholecystectomy, was done May 2, 1916. All of the gallbladder except the bottom was removed. Acute empyema of the gallbladder was found; the gallbladder had ruptured at the fundus and there was an abscess in the abdominal wall and one deep in between the gallbladder and omentum.

CASE 23 (92367).—Mrs. G. H. P., aged thirty-eight years, was examined Sept. 19, 1913. For three or four years she had had attacks of epigastric pain coming on every three or four months and lately she had had two or three each week, the last one three weeks previously. The pain was very severe, lasted several hours, and vomiting gave no relief. Morphin was required. The first operation, a cholecystostomy, was done April 24, 1913. A strawberry gallbladder was found to contain numerous small mulberry stones. There was much thickening of the common duct and the pancreas was large and hard. The patient returned for examination July, 1916, having had no trouble for three years, and then began having attacks of pain which became more and more frequent—one each day. The pain started in the right epigastrium and radiated to the back, was very sharp, and required hypodermic injections. The symptoms were precisely the same as before operation. The stools were clay colored and there was apparent slight jaundice. The second operation, a cholecystectomy, was performed July 27, 1916. Chronic empyema of the gallbladder and stones were found. The gallbladder was thick-walled and reddened, with many adhesions about it.

CASE 24 (46235).—Mrs. M. A. G., aged thirty years, was examined Nov. 23, 1910. For the past two years she had had many typical attacks of gallbladder colic. There had been no nausea, vomiting, nor residual soreness and very little digestive disturbance. A cholecystostomy was done Nov. 29, 1910. Stones were found in the gallbladder. In August, 1911, about eight months after the patient was operated on, she had begun to have a repetition of her former attacks, lasting for several days at a time, with epigastric pain, considerable bloating, and eructations of gas or food but no vomiting, chills, or jaundice. A second operation, a cholecystectomy, was done Feb. 15, 1916. A strawberry type of cholecystitis with papillomas in the walls of the gallbladder and one cholesterol stone was found.

## CHOLECYSTOSTOMY AND SECONDARY CHOLECYSTOSTOMY

CASE 25 (112866).—M. O., a male, aged forty-eight years, was examined Aug. 11, 1914. He had had attacks of typical gallbladder colic for three years, gradually becoming more frequent and severe. Hot applications afforded relief and morphin was given for severe attacks. There had been considerable bloating, vomiting at times, no jaundice, and intervals of entire freedom from any signs of trouble. Cholecystostomy was done Aug. 24, 1914. Acute cholecystitis and many stones were found. The patient returned in February, 1916; he had been well for a year and then had what he termed a "bilious attack." There was no further trouble for six months, and then a severe attack of right upper abdominal pain, radiating to his back and right shoulder, nausea, induced vomiting of bile and mucus, but no chills, fever, or jaundice. He had had several similar attacks since that time. A second operation, a cholecystostomy, was performed Feb. 17, 1916. A single mulberry stone was found in the gallbladder and pancreatitis 2 on a scale of 4.

## CHOLECYSTOSTOMY AND SECONDARY CHOLEDOCHOTOMY

CASE 26 (146436).—Mrs. J. K., aged forty-one years, was examined Nov. 23, 1915, giving a history of typical gall-stone colics fourteen years previously. Eleven days previously she had had a sudden severe attack of pain in the right epigastrium, had vomited bile, had chills, was jaundiced, and had a temperature of 99°. Jan. 7, 1915, a cholecystostomy was done. A preliminary operation was performed on account of the patient's condition. A large distended gallbladder filled with stones and a liver twice the normal size were found. A second operation, a choledochotomy, was done Feb. 17, 1916, with the removal of numerous stones from the common and hepatic ducts.

CHOLECYSTOSTOMY, SECONDARY CHOLECYSTECTOMY, AND  
CHOLEDOCHOTOMY

CASE 27 (58500).—Mrs. M., aged forty-one years, gave a history of thirteen years of typical attacks of gall-stone colic with jaundice. The first operation, a cholecystostomy, was performed Sept. 15, 1911. The gallbladder was markedly infected and contained stones. After this operation the patient was well for five years and was then seized with typical gall-stone attacks with jaundice. Sept. 5, 1916, cholecystectomy and choledochotomy were done. Cholecystitis was found with many stones in the gallbladder, but no stones in the common duct.

CASE 28 (14675).—Mrs. S., aged thirty years. She had had typical gall-stone attacks for three months, but no fever nor jaundice. Cholecystostomy was performed Nov. 30, 1910, and many small stones were found in the gallbladder. After this operation the patient was fairly well for five years, when, during pregnancy, there were occasional

belching and bloating. In the last three months she had had attacks of typical gall-stone colic with chills, but no jaundice. A second operation, cholecystectomy and choledochotomy, was performed June 17, 1916. One rounded stone at the ampulla and marked cholecystitis were found, but no stones in the gallbladder.

**CASE 29 (183209).**—Mrs. C. W., aged sixty-two years. She gave a six-year history of gall-stone colic without jaundice. Her first operation, cholecystostomy, was performed Jan. 23, 1917. A ruptured gallbladder was found containing stones and there was infection in the right anterior subphrenic space. Six months after this operation the patient had three attacks of pain with jaundice, chills, and fever. A second operation was performed May 23, 1917. Cholecystectomy and choledochotomy were done. The common duct was very thick walled and dilated, but contained no stones. There were cholecystitis, some stony débris in the gallbladder, and subacute pancreatitis.

#### OPERATIONS ON THE GALLBLADDER (NOT INCLUDING THOSE FOR CARCINOMA) IN 1916 AND 1917

##### OPERATIONS ON THE BILIARY TRACT, 2027; MORTALITY, 2.9 PER CENT

TYPE OF OPERATION	CASES	PER CENT	MORTALITY PER CENT
Cholecystectomy.....	1621	80.00	1.9
Cholecystectomy and choledochotomy.....	217	10.70	3.2
Cholecystostomy.....	82	4.00	8.5
Cholecystostomy and choledochotomy.....	27	1.30	14.9
Choledochotomy.....	39	1.90	12.9
Reconstruction of the ducts.....	28	1.38	14.0
Miscellaneous.....	13	0.60	15.3

Secondary operations.....	219	10.80	5.5
Cholecystectomy.....	120	54.70	0.8
Cholecystectomy and choledochotomy.....	32	14.60	3.1
Cholecystostomy.....	4	1.80	50.0
Cholecystostomy and choledochotomy.....	3	1.30	0.0
Choledochotomy.....	35	16.00	14.2
Reconstruction of the ducts.....	21	9.50	9.5
Miscellaneous.....	4	1.80	25.0

##### SECONDARY OPERATIONS, 219; MORTALITY, 5.5 PER CENT

	CASES	PER CENT
Cholelithiasis.....	109	49.7
Cholecystitis.....	153	69.8
Adhesions.....	148	67.5
Pancreatitis.....	441	18.7
Fistula.....	37	68.8
Strawberry gallbladder.....	34	15.5
Jaundice.....	17	7.7
Trabeculation.....	11	5.0
Stricture.....	8	3.6
Papilloma.....	7	3.1

Stones found at first operation in 154 cases; 70.3 per cent:

In the gallbladder.....	140	90.9
In the ducts.....	9	5.8
In the gallbladder and ducts.....	5	3.2



Stones found at secondary operation in 109 cases; 49.7 per cent:

	CASES PER CENT	
In the gallbladder .....	59	54.1
In the gallbladder and ducts .....	9	8.2
In the ducts .....	41	37.6

Previous operations on the gallbladder in the Mayo Clinic, 64 (29.2 per cent).

Of the 64 cases, stones were found at first operation in 51 (79.6 per cent).

Of the 51 cases, stones were found at second operation in 35 (68.6 per cent).

#### 64 SECONDARY OPERATIONS ON THE GALLBLADDER IN 1916 AND 1917

TYPE OF FIRST OPERATION	CASES
Cholecystostomy (for stones 29; cholecystitis 8) .....	37

##### TYPE OF SECONDARY OPERATION

Cholecystectomy (for stones 13; for cholecystitis 5) .....	18
Cholecystostomy (for stones in the gallbladder) .....	1
Choledochotomy (for stones in duct) .....	1
Choledochotomy and cholecystectomy (for stones or stony material in the gallbladder or ampulla) .....	8
Cholecystectomy (for cholecystitis without stones) .....	6
Cholecystectomy (for stones or stony material in the gallbladder, 2 cases; for cholecystitis without stones, 6 cases) .....	8

##### TYPE OF FIRST OPERATION

Cholecystectomy (for stones, 10; for cholecystitis, 2) .....	12
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##### TYPE OF SECONDARY OPERATION

Stones at the first operation .....	10
Choledochotomy (for stones in the ducts, 6; small ducts—adhesions, infection, 2) .....	8
Reconstruction of ducts .....	2
Choledochotomy (for partial obstruction of common duct—many adhesions and distended hepatic duct) .....	1
Reconstruction of the common duct (tremendous adhesions, but condition not sufficient to account for symptoms) .....	1

##### TYPE OF FIRST OPERATION

Choledochotomy and cholecystectomy (for stones in ducts) .....	7
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##### TYPE OF SECONDARY OPERATION

Choledochotomy (for stones and bile sand in ducts) .....	6
Reconstruction and choledochotomy (stricture of common duct and tumor of cystic duct) .....	1

##### TYPE OF FIRST OPERATION

Choledochotomy and cholecystectomy (for stones in ducts and bladder) .....	3
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##### TYPE OF SECONDARY OPERATION

Choledochotomy (stone in the common duct) .....	1
Cholecystectomy (cholecystitis with multiple small cysts in the mucosa) .....	1
Cholecystenterostomy (tense gallbladder filled with bile—fistula arising from the common duct—infection of the gallbladder—much oozing from all the tissues) .....	1

##### TYPE OF FIRST OPERATION

Choledochotomy (stones in the hepatic duct) .....	2
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##### TYPE OF SECONDARY OPERATION

Choledochotomy (greatly dilated ducts, no stones, pancreatitis, 3) .....	1
Partial cholecystectomy (empyema of the gallbladder, no stones, a great many adhesions) .....	1

# **SYMPTOMS FOLLOWING OPERATIONS ON THE BILIARY TRACT      131**

<b>TYPE OF FIRST OPERATION</b>		<b>CASES</b>
Drainage of a subphrenic abscess (preliminary to further operation).....		1

<b>TYPE OF SECONDARY OPERATION</b>		
Cholecystectomy and excision of the sinus tract for ruptured gallbladder and stone in the sinus tract.....		1

<b>TYPE OF FIRST OPERATION</b>		
Reconstruction of the hepatic duct (biliary fistula, dense adhesions).....		2

<b>TYPE OF SECONDARY OPERATION</b>		
Reconstruction of the ducts (hepatic duct opened at the point of union with the stomach—stone removed from the hepatic duct).....		1
Opening in the hepatic duct much contracted; this was enlarged and the anastomosis separated.....		1

<b>TYPE OF FIRST OPERATION</b>		
Choledochotomy (stones in hepatic duct).....		2

<b>TYPE OF SECONDARY OPERATION</b>		
Choledochotomy (greatly dilated ducts—no stones—pancreatitis, 3).....		1
Partial cholecystectomy (empyema of gallbladder—no stones—great many adhesions).....		1

<b>TYPE OF FIRST OPERATION</b>		
Drainage of subphrenic abscess (preliminary to further operation).....		1

<b>TYPE OF SECONDARY OPERATION</b>		
Cholecystectomy (excision of sinus tract of ruptured gallbladder and stone in sinus tract).....		1

<b>TYPE OF FIRST OPERATION</b>		
Reconstruction of hepatic duct (biliary fistula—dense adhesions).....		2

<b>TYPE OF SECONDARY OPERATION</b>		
Reconstruction of duct (hepatic duct opened where it was united to stomach and the stone removed).....		1
Reconstruction of duct (the opening in the hepatic duct was much contracted and was enlarged—anastomosis separated).....		1

<b>TYPE OF FIRST OPERATION</b>		
Cholecystectomy (for stones, 10; for cholecystitis, 2).....		12

<b>TYPE OF SECONDARY OPERATION</b>		
Stones at the first operation.....		10
Choledochotomy (for stones in ducts, 6; small ducts—adhesions—infection, 2).....		8
Reconstruction of ducts.....		2
Choledochotomy (for partial obstruction of common duct—many adhesions and distended hepatic duct).....		1
Reconstruction of common duct (tremendous adhesions, but condition not sufficient to account for symptoms).....		1

<b>TYPE OF FIRST OPERATION</b>		
Choledochotomy and cholecystectomy (for stones in ducts).....		7

<b>TYPE OF SECONDARY OPERATION</b>		
Choledochotomy (for stones and bile sand in ducts).....		6
Reconstruction and choledochotomy (stricture of common duct, and tumor of cystic duct).....		1

## TYPE OF FIRST OPERATION

Choledochotomy and cholecystostomy (for stones in ducts and gallbladder) . . . . . 7

## TYPE OF SECONDARY OPERATION

Choledochotomy (stone in common duct) . . . . . 1  
 Cholecystectomy (cholecystitis with multiple small cysts in mucosa) . . . . . 1  
 Cholecystenterostomy (tense gallbladder filled with bile—fistula arising from common duct—infection of gallbladder—much oozing of all tissues) . . . . . 1

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## THE LIVER AND ITS CIRRHOSES\*

W. J. MAYO

The liver is the central metabolic laboratory of the human body responsible for the final preparation of nutritive material for conversion into tissue-building and energizing substances. A brief review of some of its anatomic and physiologic characteristics may not be out of place. The weight of the average liver in man is 50 ounces, with a normal variation of about 10 per cent. It may be assumed, therefore, that a liver weighing more than 55 ounces is increased in size and might properly be called hypertrophic, and one weighing less than 45 ounces might be called atrophic, unless such difference could be explained by the size, above or below the normal, of the person. If the weight of the liver is an indication of its metabolic activities, the liver of the female should be larger in proportion than that of the male, made so by the necessity of taking care of herself and her unborn child. As a matter of fact, the liver of the female is only one-fortieth of the body weight, while that of the male is one-thirty-sixth of the body weight. The hepatic artery is relatively a small vessel and has no corresponding veins. It is supposed to nourish the liver itself and, so far as its framework, the biliary channels, and the gallbladder are concerned, this is undoubtedly true; but I have not seen anatomic proof that the liver cells are nourished by the hepatic artery. It would appear that the liver cells, in the process of acting on the blood brought to them through the portal circulation, receive nourishment direct, and that there is no distinction in this respect between the blood of the hepatic artery and that of the portal vein.

The portal system is made up of the gastromesenteric veins and the splenic vein, and it should be noted that the normal splenic vein carries to the liver from one-eighth to one-sixth of the total quantity of portal blood. The enlarged spleen has vessels in accordance with its size. The large spleens in certain splenomegalias may have vessels the size of the superior mesenteric artery and veins. This is most important,

\* Reprinted from *Jour. Am. Med. Assn.*, 1918, lxx, 1361-1364.

as it indicates that removal of the spleen relieves the liver of a large load of blood and, as shown by the results of splenectomies, this diversion to the general circulation may be sufficient to relieve the subnormal liver of its overload and enable the patients to return to a fair degree of health in otherwise fatal cases. Splenectomy establishes a new principle of treatment, namely, a reduction instead of a diversion of portal circulation, as accomplished in the experimental Eck fistula and the Talma, Drummond, and Morison operation. The stomach and rectum each have a double vascular circulation, portal and systemic. Double ligation and division of the inferior mesenteric artery and vein where they cross the left common iliac vein or just beyond at the promontory of the sacrum, where the artery takes the name of the superior rectal would greatly reduce the portal circulation. The artery is as large as the brachial, and in two-stage operations for cancer of the rectum experience has shown that an enormous compensatory circulation is established with the general circulation through the middle and external hemorrhoidal vessels. Some effect might be produced by tying the superior coronary vessels of the stomach, thus increasing the return circulation about the esophagus, but this would be relatively unimportant and might increase the tendency to gastric hemorrhage.

To the liver has been given wonderful power of regeneration. If a considerable portion of the organ is removed, it will be restored by the remaining liver cells. Such regeneration has not been given to any other organ in the human body. When the necessity for work compensation is thrown on other organs, it is by hypertrophy of preëxisting elements, not cell hyperplasia, that the stress is met. The outstanding feature of the hepatic cell is that there is no differentiation of the cells. Each liver cell is exactly like every other liver cell, and each normal liver cell is fully capable of bearing its portion of the work, here again differing from every other similar organ in which groups of specialized cells are to be found.

#### FUNCTIONS OF THE LIVER

Our knowledge of the function of the liver is very imperfect. We have learned something from experimentation. About postmortem conditions we know a great deal, but, as the liver cannot be removed in life, and as no attempt is made to remove any considerable portion of it except for disease, which vitiates the testimony, its functions have been most difficult to ascertain. The liver has five chief functions: (1) The

metabolism of carbohydrates; (2) the metabolism of proteins; (3) the metabolism of fat; (4) the production of bile, and (5) the defense against bacteria, protozoa, and toxic chemical substances.

1. The glycogenetic function of the liver is most important in the final conversion and storage of carbohydrate derivatives in a form from which energy is most readily produced. The monosaccharids might be called the body coal, which heats and energizes, the ash end-product, the carbon dioxid, being carried out of the system by the ventilating function of the lungs. Sugar is a threshold body always existing in the blood, but appearing in the urine only when in excess of a definite percentage.

2. The amino-acids from protein digestion, of which eighteen have been described, are carried to the liver by the portal vein and, among other changes, the nitrogen-containing portion of the molecule is there converted into urea. The conversion of the nitrogen-containing portion of the amino-acids into urea is not carried on exclusively in the liver, but the liver seems to have a greater capacity than any other tissue for this reaction. Experimental work on the development of urea is most interesting and indicates that possibly the blood urea may act as a hepatic hormone in relation to protein metabolism. Cushny states that urea is not a threshold body in the blood; that is, it is always to be found in the blood and in the urine. The amino-acids are used in tissue building. They are also converted into fuel and energy-producing substances. Plummer and Kendall have shown that cellular activity is sparked, so to speak, by the thyroid secretion, hyperthyroidism over-energizing this activity, and resulting in a burning up of the tissues.

3. The fat function of the liver is not well understood. We know that sugar and fat are stored temporarily in the liver, ready for immediate use. It is probable, under certain circumstances, that carbohydrates are converted into fat in the liver. It has been shown that by forced overfeeding of carbohydrates the liver of the goose may be caused to become enormously fat, constituting a well-known Teutonic delicacy. Osler has pointed out that the carbohydrate value of beer, although small, is sufficient, when enormous quantities are drunk, to cause an immense storage of fat in the human liver, and that when this fat exists in connection with a deposit of connective tissue the portal cirrhosis which follows will develop a hypertrophic instead of an atrophic liver. In acute stress, such as occurs in phosphorus and chloroform poisoning, and massive infections, the liver may undergo a most rapidly fatal fatty

degeneration. Its usual response to destructive insults appears to be acute fatty degeneration. In these first three functions, namely, the metabolism of carbohydrates, proteins, and fat, the liver completes a process started in the gastro-intestinal tract. In the next two—the bile and defense functions—the spleen is associated with the gastro-intestinal tract.

4. It is difficult to state whether the production of bile is purposeful or a waste which contains by-products valuable in intestinal digestion. The bile-pigments are derived from destroyed red corpuscles carried to the liver, partly from the spleen. At one time the red blood-cells of the body were supposed to be completely regenerated in from seven to ten days, the estimation being based on the total amount of pigments excreted in the bile. Recent investigations, however, cause some doubt regarding the accepted opinion that the bile pigments are all derived from destroyed red cells, and indicate that the red cells have a much longer life. The latter view agrees with the known results of blood transfusion in the anemias. When enormous quantities of blood are destroyed, as in hemolytic icterus, the liver, as well as the spleen, becomes greatly enlarged—a condition that has been confused with biliary cirrhosis. Accumulating evidence, however, goes to show that, while such a liver may contain an increased amount of connective tissue, it is not necessarily related to the biliary channels, and to a very great extent the enlargement may be looked on as a work hypertrophy with hyperplasia of the liver cells. An interesting constituent of the bile is the lipid cholesterin; a certain amount of cholesterin is always to be found in the blood, but the amount excreted in the bile varies greatly with the condition of the patient. In the pregnant female, as reported by Aschoff, cholesterin is greatly increased; this suggests its relation to gall-stones, which are four times as common in women as in men, at the same relative ages, and in 90 per cent of the female patients with gall-stones the first symptoms are related to a pregnancy.

5. The defense function of the liver is most important. Bacteria are constantly being carried to the liver from the portal circulation, and pigments of these slaughtered bacteria are found as non-hematogenous hepatic pigment areas (Adami). The spleen strains out many bacteria, as in typhoid, and protozoa, especially the plasmodium of malaria and the spirochete of syphilis; but it may be unable to destroy these organisms, and they are sent to the liver for destruction. It seems fairly clear that, at least so far as portal cirrhosis is concerned, it is related to

he defense function; the liver, losing power to absorb and eliminate diffuse poisons, attempts to encapsulate them, thus introducing the connective tissue. The spleen has been compared by Rowntree to the glomeruli of the kidney, and the liver to the tubules, the one straining out the degenerated cells, microorganisms, and poisons, and the other acting on the material brought to it. The interrelated pathologic condition of the spleen and liver follows closely this interrelation of function.

#### CLASSIFICATION OF CIRRHOSIS

The foregoing most prominent facts connected with the anatomy and physiology of the liver have been reviewed with the idea of throwing some light on the connective-tissue diseases of the organ. First inaptly called cirrhosis by Laennec, on account of a tawny or yellow color which sometimes exists, cirrhosis is a term applied indefinitely and indiscriminately to almost any condition of the liver which is not understood, but in which there is an excess of connective tissue. The outstanding feature of all liver changes, the result of chronic irritation without regard to cause, is the deposit of connective tissue. This is well shown in the local cirrhotic processes which may accompany cancer, syphilis, and tuberculosis of the liver.

The pathologic classifications are based on morphology, and the morphologic pictures are sometimes differently interpreted by the various authorities. To one who makes an attempt to understand the cirrhosis and who is interested in the living rather than the dead body, the pathologic descriptions are certainly far from illuminating. It is sometimes of benefit to be an amateur, in that an amateur may be able to see more clearly the larger elements, which are often lost in details; in other words, a better perspective is obtained. Generally speaking, fundamental types of cirrheses may be distinguished; the others represent combinations or variations, rather than entities.

The two types are:

1. Portal cirrhosis, in which the chronic irritants, probably biochemical substances, are introduced through the portal vein, and in which circulatory disturbances are the most prominent clinical features, causing gastric hemorrhages, and especially ascites. Jaundice is seldom present and only as a terminal symptom.
2. Biliary cirrhosis, in which jaundice is clinically the chief symptom, ascites being absent or, if present, being a terminal condition, with the evidence pointing to an infectious cause.



In portal cirrhosis the connective tissue is introduced about the radicles of the portal vein, and in biliary cirrhosis, about the bile-ducts. In both portal and biliary cirrhosis the spleen is often enlarged and has a causative relation in many cases, such as the terminal portal cirrhosis of the splenic anemias—the so-called Banti's disease.

I have never seen a case I could call Hanot's cirrhosis, and, so far as I know, this type of cirrhosis has no pathologic basis and little clinical evidence to support its existence. The large majority of cases that have taken the term of Hanot's cirrhosis are either hemolytic icterus or the ordinary type of biliary cirrhosis. As a matter of fact, hemolytic icterus, primarily a splenic disease with a work hypertrophy of the liver, has been confused with biliary cirrhosis and, as gall-stones with recurring exacerbations of infections have existed in something like 60 per cent of the cases in which we have removed the spleen for the cure of hemolytic icterus, this confusion has not been entirely without excuse. If we constantly bear in mind that, without regard to the nature of the irritant, the response in the liver is connective-tissue formation, and that this may involve the whole liver or that it may exist locally, it may readily be seen where confusion has arisen. While typical portal cirrhosis, on the one hand, and typical biliary cirrhosis on the other, are well defined, atypical forms exist from mixed causes, as portal cirrhosis with secondary biliary cirrhosis from gall-stone infections.

If hemolytic icterus is split off from the cirrhotoses, and if it can be shown by further investigations, which our somewhat limited experience leads me to believe, that the enlargement of the liver which often exists in hemolytic icterus is a work hypertrophy and that the connective-tissue formation present is not specific, much will have been accomplished in clearing up a vexed question.

Comparatively little work has been done on portal cirrhosis since the eighties, but during that period many interesting papers were written, especially by the French and English. Hilton Fagge calls attention to a number of cases in which persons apparently in perfect health died suddenly from accidental causes and were found at necropsy to have had an extensive cirrhosis of the liver, suggesting some unknown factor not properly estimated. At operation I have occasionally found extensive cirrhosis of the liver unrelated to the condition which called for the operation and apparently not of immediate clinical importance.

## COMPARISON OF PORTAL AND BILIARY CIRRHOSIS

It is probable that the relation of stimulants to cirrhosis of the liver, at least in this country, has been exaggerated. I have seen a considerable number of cases of portal cirrhoses in non-alcoholic young persons. Fagge shows that in Guy's Hospital for twenty-five years 14 per cent of those dying from portal cirrhosis with ascites had complicating tuberculous peritonitis. Cheadle and others have shown that, while the Laennec type of atrophic cirrhosis stands at one end of the group, representing the typical gin or hobnail cirrhosis of the liver, as many cases are to be found in which the weight of the liver is increased as there are those in which it is diminished, and the belief that such huge livers finally contract down to the Laennec type is unfounded. It is, of course, quite probable that, in the hepatitis which early accompanies the deposit of connective tissue, the liver would be somewhat enlarged before contraction. But that this is at all true of the massive livers, and especially of those containing quantities of fat, as seen in the beer drinker, cannot be credited. Our better understanding of the atrophic type of portal cirrhosis has led us to underestimate the frequency with which the cirrhotic liver is increased in size and weight. In biliary cirrhosis the liver is always enlarged. The margin of safety in the liver is very great. The patient with portal cirrhosis rarely dies from insufficiency of hepatic tissue, but death is usually brought about through changes in the circulation and secondary complications, while in biliary cirrhosis death results from chronic jaundice and cachexia. The establishment of compensatory circulation by which blood would be passed from the portal vein around the liver into the general circulation, as advanced and pictured by Talma, Drummond and Morison, has given marked palliation in suitable cases. Sappey has most accurately described the venous avenues by which such compensatory circulation is brought about through nature's unaided efforts. Eck's fistula, that is, the establishment of a bypath between the portal vein and the vena cava, is purely experimental. It is of interest that in all the cases I have seen in which portal cirrhosis accompanied splenic anemia the cirrhosis was of the atrophic type of Laennec.

In 51 cases of splenic anemia in which we have removed the greatly enlarged spleen, the relief to the portal circulation has been immediate. In those cases in which cirrhosis was present the ascites has now disappeared, and several patients have lived for years, one for more than

seven, in excellent health. The evidence here points to the fact that the original poison was carried to the liver from the spleen and theoretically is probably a protein derivative, filtered from the blood. But in five cases of portal cirrhosis with ascites, in which I removed the enlarged spleen, the four patients who recovered were greatly improved both as to their general condition and as to the relief of the ascites. On first thought it seemed probable that in the removal of such a spleen I had checked the source of poisoning. On further consideration another explanation appears possible or even probable. With the removal of the spleen, all the blood from the general circulation, which otherwise would have been sent to the liver through the splenic vein, was prevented from going there, and in this manner sufficient blood had been diverted from the liver to relieve the portal circulation. Possibly both views are more or less correct. The results in these cases should encourage us to splenectomize in suitable cases of portal cirrhosis in the future, especially when the spleen is enlarged.

Biliary cirrhosis, of the obstructed or acutely infected type, is easily understood. It exists in connection with gall-stones, particularly those in the common duct, and jaundice is an early and continuous feature. In many of these cases, however, the patients are not cured by the removal of gall-stones and biliary drainage. More or less permanent damage has been done to the ducts, resulting in chronic areas of infection and often in deposits of stones in the bile-ducts, until thousands of such stones may be found in the liver. A second type, which is not so well understood, accompanies certain chronic biliary infections. In these it would appear that either primary hematogenous infection of the bile-ducts took place or that there was an extension from a chronically infected gallbladder to the ducts. Rosenow's work in revealing the specificity of bacteria, and in showing that the bacteria, usually streptococci, are to be found in the walls of the gallbladder and ducts and not in the bile, is most important. Large, soft lymphatic glands are usually to be found along the common duct and in the fissure of the liver. In chronic biliary cirrhosis the liver is large and the walls of all the biliary ducts are extremely thick. In one instance the lumen of the common duct was reduced at least one-half by the deposit of connective tissue in the wall of the duct. Every grade of biliary cirrhosis may be found in this chronic type, which is much more liable to be accompanied by an enlarged spleen than those dependent on the more acute infections of the common duct. Not infrequently chronic pancreatitis will be pres-

ent from coincident infection. I have seen cases of this description in which there was apparently much improvement by prolonged biliary drainage to the surface, or by a cholecystogastrostomy or cholecystoduodenostomy; but as the clinical course of these patients is very chronic, I am not at all sure that cause and effect are properly related. In five cases of this type, in all of which the spleens were enlarged and the patients were more than thirty-five years of age, I performed splenectomy. All were improved, the jaundice was greatly reduced, though it had not entirely disappeared in any case, and the liver remained more or less enlarged. There are two possible explanations of this improvement: (1) The source of the chronic infection may have been focal at some point in the body, and the toxic material resulting may have been continuously strained out in the spleen and sent to the liver, continuing the infection there. Such cases are occasionally seen in diseases that follow infectious diseases, for example, pneumonia. (2) When the spleen was removed, there was a large reduction in the necessary work to be performed by the liver.

The confusion which has arisen between biliary cirrhosis and hemolytic icterus has somewhat of a parallel in the failure to differentiate those ascites due to polyserositis (Concato's disease) and portal thrombosis from portal cirrhosis. Fagge states that for every three cases of portal cirrhosis with ascites, he saw one of ascites from polyserositis. Concato's disease may be recognized by the thick white peritoneum, by the intestines with greatly shortened mesentery clustered about the spine, and by the encasement of the liver and spleen in a thick white fibrous membrane. Free fluid is usually to be found in both pleural cavities. Pick's syndrome often exists, in which pericardial adhesions hamper the heart's action. The fact that, in some of these cases, the liver is completely encapsulated leads the uninitiated to believe that some form of cirrhosis is present, but, on excision of the strangling membrane, the liver will be found normal.

Warthin<sup>11</sup> has pointed out that thrombosis of the portal vein or some of its branches occasionally occurs with ascites, being a chronic malady accompanied by liver changes and splenomegalia, and usually confused with portal cirrhosis or splenic anemia.

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[ABSTRACT\*]

## THE SURGICAL TREATMENT OF THE CIRRHOSES OF THE LIVER AND THEIR COMPLICATIONS

W. J. MAYO

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It seems probable that when there is great enlargement of the spleen with the cirrheses, the removal of the spleen may, by cutting off the source of much blood, so reduce the portal circulation as to bring it to a point where the cirrhotic liver can carry on its function, or the measure of improvement may come about by preventing those irritants ordinarily filtered out in the spleen from reaching the liver. Probably both are factors as in splenic anemia.

In our series of 52 splenectomies for splenic anemia there were a considerable number in which the liver showed portal cirrhosis. In five advanced cases of this type the ascites completely disappeared after splenectomy, and the patients have gained so greatly in strength as to be said to be cured, and have been able to work for a number of years. When we consider that the splenic vein under normal conditions is about one-sixth the diameter of the portal vein, and that in the enlarged spleen the vessels are correspondingly increased in size, it will readily be seen that the removal of the spleen in suitable cases affords a quick and certain method of relieving the portal circulation.

I have removed the greatly enlarged spleen in 6 cases of portal cirrhosis, two of the alcoholic type. One patient died too soon after the operation to show benefit, but the other 5 were greatly relieved. As the operation of splenectomy, which prevents the blood from reaching the portal vein, is not one of great difficulty, it would seem to be even superior, in suitable cases, to the Talma-Drummond-Morison method of diverting the blood from the portal to the systemic circulation through the venous compensatory channels of Sappey.

The relief of the portal circulation by reducing the amount of blood

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which enters the liver may also be accomplished readily by the ligation of the inferior mesenteric or superior rectal vessels. A small incision is made through the peritoneal covering of the right side of the sigmoid mesentery and the vessels are doubly ligated and divided, with resuturing of the peritoneal incision. Considerable experience in such ligations, made in connection with permanent colostomy as the first step of a two-stage removal of the rectum for cancer, has shown that an immense collateral circulation is established through the middle and external hemorrhoidal vessels, and that the bleeding at the second stage, done two weeks later, is so greatly increased as to become troublesome. The coronary arteries of the stomach could be ligated safely, but in the cirrhoses this procedure might increase the ever-present danger of gastric hemorrhage.

We have done the Talma-Drummond-Morison operation 28 times with 4 operative deaths. Eight of the patients have died at various dates following operation; the remainder have been more or less benefited; five report their condition as good. Various technics have been employed. In a few cases subcutaneous silk drains were placed with one end entering the peritoneal cavity. In two the internal saphenous vein was employed in a similar manner. All in all, we have found that the easiest and safest method is to draw the omentum up through the peritoneum into the incised rectus muscle, suturing it in that position, and closing the fascia carefully over it. On several occasions we have gone down a second time in the vicinity of the previous operation, with a view of increasing the omental attachments, and have found such extensive compensatory circulation, almost entirely venous, that we were obliged to desist, and even with difficulty controlled the hemorrhage. The Eck fistula, which diverts directly from the portal circulation to the vena cava, while occasionally successful experimentally, has as yet no practical value.

Biliary cirrhosis dependent on infections from gall-stones will usually be found complicated by chronic pancreatitis and enlargement of the spleen. The remedy which suggests itself is removal of the gall-stones and drainage of the biliary ducts. The operation should be done as early as possible, before extensive secondary duct infections occur, which lead to deposits of calculi in the various liver ducts, such as are occasionally found in the terminal stages of the disease. The type of biliary cirrhosis which depends on chronic infection, and results in a reduction in the lumen of all the ducts of the liver, presents a difficult problem.

In several instances, when it seemed indicated, prolonged drainage of the gallbladder was instituted. This apparently has been of benefit to the patient and suggests that the source of bacterial infection was in the gallbladder. We have, in selected cases of this kind, made a cholecystogastrostomy or a cholecystoduodenostomy, as they are equally as efficient and are less troublesome to the patient than the cholecystostomy. Some of the patients have been greatly benefited; but as a considerable percentage have had coincident chronic pancreatitis which may have interfered with common duct drainage, some part of the improvement may have been derived from relief of this interference.

I have removed a large spleen in five instances in which there was associated advanced biliary cirrhosis, and the results have been extraordinarily good, although none of the patients can be said to be cured. Whether the splenectomy, by reducing the amount of work, acted as a relief to the disturbed liver-function, or whether it was the means whereby bacteria, reaching the blood-stream from focal infections in the body, were diverted from the liver, I am unable to determine.

In conclusion I would call attention to splenectomy and similar procedures as a ready means of reducing the portal circulation for the purpose of relieving the subnormal liver of its overload.



## SECONDARY TUBERCULOUS PERITONITIS: ITS CAUSE AND CURE \*

W. J. MAYO

Tuberculous peritonitis is not a primary disease, but, like septic peritonitis, is symptomatic, having its origin in some local focus of infection. The most common sites of such local foci are the fallopian tubes in women, some part of the intestinal tract in both women and men, and the lymphatic glands and channels, especially in children. Occasionally the primary focus will be found in the stomach, the spleen, the liver, the gallbladder, or the genito-urinary tract. To consider tuberculous peritonitis an entity, or to treat it as such, leads to confusion, whereas if it is looked on as a secondary process, due to some primary focus, we are led to search for the primary focus and to direct treatment leading toward cure.

### REMOVAL OF THE LOCAL FOCUS

In 1904, in the Address on Surgery presented before the Mississippi Valley Medical Association, I called attention to the fact that when the local lesion could be found and removed in operating for so-called tuberculous peritonitis, a cure might be expected in a much higher percentage of cases than by the performance of a simple laparotomy, with or without medication, the latter being unsatisfactory at best. At that time I was particularly interested in the relation of tuberculosis of the fallopian tubes to tuberculous peritonitis, and reported in detail some cases in which simple laparotomy with the evacuation of fluid had been carried out from three to seven times with a reaccumulation of the fluid and failure to cure, followed by prompt cure after the removal of the tuberculous tubes. Murphy pointed out that in tuberculosis the fimbriated extremities of the fallopian tubes were usually open, quite the opposite from the condition that exists in gonorrheal infection of the fallopian

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tubes, in which they are closed. In gonorrheal infections, therefore, pus tubes are common, while in tuberculosis, tubal retention is much less common, and the material from the tuberculous process passes out from the fimbriated extremity of the tube into the abdominal cavity, causing a more or less generalized peritonitis. Such peritonitis is essentially a conservative process, leading to the destruction of the noxious agents. When the source of the infection can be removed, the peritoneum returns to normal. At a subsequent laparotomy the peritoneum will be shown to be quite free from disease and without signs of past involvement, beyond adhesions in some locality that had been subjected to prolonged infection, as in the vicinity of the primary lesion. It is true that simple laparotomy sometimes cures the peritonitis when tapping would be of no avail, because when the fluid is completely removed from the peritoneal cavity, for example, by operation, the fimbriated ends of the tubes, which had been mechanically separated by the fluid from the surrounding tissues, may become adherent to neighboring structures, thus closing the ends and preventing further leakage. Under such circumstances tubal retention of the tuberculous products results, and these pus tubes may be recognized as gradually increasing masses in the pelvis. Further experience developed the fact that the tube thus closed became surrounded by a mass of adhesions, and occasionally, in the course of long months or years, a spontaneous "near" cure resulted. The tubal content became caseated and was rendered more or less innocuous, with the gradual disappearance of the pelvic masses, but with permanent fixation of the pelvic organs. The ciliated epithelium of the tubes, like the ciliated epithelium of the pulmonary tract, is very susceptible to tuberculosis. Whether the tubercle bacilli reach the tubes primarily through some other focus in the abdominal cavity and then gravitate into the pelvis, infecting the tubes, or whether they pass directly by way of the vagina and uterus or through the lymphatics, is a mooted question.

Tuberculosis of the endometrium is rarely found in the menstruating uterus. When tuberculosis involves the endometrium, it is usually found in children before menstruation begins or in women after the menopause. If it occurs during normal menstrual life, menstruation will have ceased, although in its place there may be a bloody discharge, the result of the tuberculous lesions.

Fourteen years of experience since the publication of these observations has confirmed them in every respect, and it may be said that in

tuberculous peritonitis which is the result of tubal tuberculosis, the removal of the fallopian tubes may be expected to cure, unless other incurable tuberculous lesions coexist. It is not at all necessary in such cases to remove the ovaries or the uterus, as their involvement is only superficial, and in no way different from that shown in the peritoneal coverings of the intestines and the other viscera.

Our knowledge of tuberculous peritonitis, the result of tubal disease, is fairly adequate; but when the local lesion is elsewhere, great difficulty may be experienced in locating and removing the primary source of the peritoneal infection. Rarely, in our experience, has the appendix alone been the cause of tuberculous peritonitis. Tuberculosis of the ileocecal coil, including the appendix, especially of the hyperplastic type, is often accompanied by tuberculous peritonitis, which, as a rule, is limited to the immediate vicinity of the primary disease, and the removal of the involved bowel promptly cures. This is equally true of localized tuberculosis of the small intestine.

We have encountered a considerable number of cases of peritoneal tuberculosis, confined to the region above the transverse colon, in which the lesion was particularly marked in the vicinity of the gallbladder and the pyloric end of the stomach. In most of these cases the gallbladder, which had shown cholecystitis, was removed; but we have not been able to determine that there were tubercle bacilli in the gallbladder or its contained secretion, nor have we found local lesions that might have been the result of a focus in the liver. However, such patients, without exception, have quickly and permanently recovered. It is questionable whether such recovery might have taken place without the removal of the gallbladder.

Barker estimates that 50 per cent of cases of tuberculous peritonitis are due to bovine tuberculosis. It is interesting to note that the English Commission on Tuberculosis (1911) showed that tuberculous peritonitis was due to bovine tuberculosis in nearly 47 per cent of the cases, and the German commission showed it to be due to this cause in 63 per cent. It is possible that bovine tuberculosis gives a more favorable prognosis than human tuberculosis.

#### SIMPLE LAPAROTOMY

The possibilities of the cure of tuberculosis of the peritoneum by simple laparotomy, when the local focus cannot be discovered and removed, are limited to the ascitic forms of the disease. It may at least

æ said that an open operation, with careful removal of all fluid, with or without medication, has therapeutic value. It would seem, however, that the surgical profession has been overenthusiastic in its praise of the simple operation. The fibroplastic types are benefited only if there are sacculations containing fluid; but operation is contraindicated when the adhesions fill the entire abdomen without collections of fluid, or if the collections consist of multiple small pockets filled with turbid tuberculous exudate containing pus. Operation in these cases with separation of adhesion is of little value, and often results in intestinal fistula. Fortunately the adhesion type of tuberculosis of the peritoneum giving rise to the swollen, hard (wooden) abdomen are most favorable for spontaneous cure.

It seems probable that tubercle bacilli alone tend to produce tuberculous peritonitis with a minimum of adhesions, and that to a considerable extent the adhesions are the result of a mixed infection; but as the pyogenic bacteria that are admitted with the tubercle bacilli are shorter lived, they disappear, leaving only the tubercle bacilli to be discovered at the time of operation. In several subacute cases of this description I was able to find not only a mixed infection, but also localized pockets of pus, containing colon and other bacteria having their origin in the intestinal tract. Later, these pyogenic bacteria would have disappeared and only the tuberculous process would have been discoverable.

Koenig, in 1890, was the first to call attention to the value of simple laparotomy in the treatment of tuberculous peritonitis, reporting 139 cases with 84 recoveries. How long these recoveries lasted was not recorded. Shattuck, in 1902, showed a medical mortality of 68 per cent and a surgical mortality of 37.5 per cent in 98 cases of tuberculous peritonitis at the Massachusetts General Hospital. Two-thirds of his patients were females. Wunderlich, in 1899, collected 344 cases in which the patients were treated surgically, and 176 of whom were traced. At the end of three years only 26 per cent of these were in good health. Bircher, in 1907, collected 1295 surgical cases, and found 69 per cent of immediate cures; but only 31 per cent of these patients were well after a year or more. Osler noted 131 females to 60 males. Curiously enough, while all the surgical cases, and for that matter all the medical cases observed, show an excess of females over males, the postmortem findings show peritoneal tuberculosis to be more common in the male.

The English school has strongly advocated drainage following laparotomy for tuberculous peritonitis; but drainage has been almost

abandoned in this country on account of the frequency with which mixed infection has followed, often with fistulas which became feculent. After laparotomy, as a rule, there is a reaccumulation of the fluid, which is said to have a higher opsonic index and therefore a higher resistance against tuberculosis than the fluid that was originally removed. The fluid reaccumulated directly from the blood has marked sterilizing properties.

It should not be forgotten that tuberculous pleurisy or tuberculous pericarditis may exist in conjunction with tuberculous peritonitis. When there is doubt as to whether or not an ascites is due to tuberculous peritonitis, the finding of fluid in one or both of the pleural cavities is strong but not positive evidence, as the same condition is found in Concato's disease. Chronic irritative peritonitis or chronic proliferative polyserositis, as described by Concato, may be local or general. The spleen or the liver, or more often both, may be encapsulated, or the entire abdominal cavity may be involved, with most extraordinary shortening of the mesentery of the intestine. The contracted intestinal tract may be covered with an adhesive membrane and be drawn close to the spine. Chronic ascites is usually marked. The peritoneum, in the later stages, may be a quarter of an inch or more in thickness and of a white color. In the more extensive cases, both pleural cavities are involved, and often the pericardial sac as well.

Pick's disease is undoubtedly only a syndrome, a subdivision of chronic proliferative serositis, in which the chief manifestation is cardiac crippling, due to pericardial adhesions, although Pick believes that the pleural and peritoneal involvements are results of changes brought about in the circulation by interference with cardiac action. In none of the cases of chronic proliferative peritonitis that I have seen was the diagnosis made until the abdomen was opened, and I am confident that in my earlier experience the condition was confused with tuberculous peritonitis. However, some observers believe that tubercle bacilli are the causative factor. It is altogether probable that chronic proliferative polyserositis is frequently, if not usually, confused with the ascitic forms of tuberculous peritonitis. Except for the temporary relief of the ascites, laparotomy is of no value in Concato's disease. It is said that the fluid aspirated may be distinguished by chemical analysis from tuberculous fluid; this has not been confirmed in our cases. As to the frequency of Concato's disease, Fagge states that he saw one case of ascites from this cause to three of cirrhosis of the liver.

It will be seen from this brief summary that the cases of tuberculous peritonitis, in which surgical treatment promises to be of great aid, rather naturally divide themselves into two groups: First and most favorable are those cases in which a definite anatomic portion or viscus of the peritoneal cavity is involved, such as the fallopian tubes, the ileocecal coil, and the appendix, which can be removed. Second, and less favorable, are those in which the peritoneal cavity contains a considerable quantity of fluid, occupying either the entire peritoneal cavity or a large part of it, or in which the fluid is contained in loculi composed of peritoneal adhesions, dividing the peritoneal cavity into compartments containing fluid.

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## ACUTE PERFORATIONS OF THE ABDOMINAL VISCERA\*

W. J. MAYO

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There is a certain surgical philosophy which not only interprets disease conditions from the clinical and pathologic standpoint, but also endeavors to arrange facts in orderly array, to follow the natural history of the disease and its relations to other disease processes of which it either is a part or with which it may become associated as a cause or an effect. Such philosophy does not follow a direct pathway, text-book fashion, but strives rather to secure a perspective of the devious paths along which knowledge of disease in general has advanced; its ultimate goal is the full exploration of the breadth as well as the length of the road. In this manner, I believe, we may acquire wisdom.

Our knowledge of acute perforations of the abdominal viscera had its origin largely in perforative appendicitis, although the first perforations studied were those of the stomach. To the late Reginald Fitz of Boston, we owe our earliest organized knowledge of three most important surgical conditions: The relation of appendicitis to general septic peritonitis, of perforations of the pancreas to fat necrosis, and of the diverticulum of Meckel, its infections and perforations, its frequent occurrence in the young, and the ironing-out process of development and gas pressure by which Meckel's diverticulum becomes less evident in the old. The work of Fitz was done largely postmortem. His investigations connected cause with effect, but as they began in the dead and ended in the grave, an exaggerated notion of the fatality of acute perforations in general was obtained. The evidences of perforations were almost lost in the peritonitis which ensued and which caused the death of the patient. In speaking of acute perforations, we visualized the dead man with a general septic peritonitis.

The slow process of developing a living pathology was taken up by the

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surgeon, and little by little the ravages of the fatal septic peritonitis were separated from the cause. We began to see that not all perforations ended fatally and that many factors came into play which might permit of spontaneous recovery from any particular perforation. These factors concerned the quantity and virulence of the leakage from the perforating organ, the general resistance of the patient, and the local anatomic situation of the perforation with relation to the prospects of limiting by adhesions the spread of the contamination and resulting peritonitis. The mechanical relations of the perforated viscus to the omentum, colon, and other peritoneal covered organs as well as to the abdominal wall, which would permit of barricades against further spreading, and especially those mechanical factors which prevent contamination of the small intestine with its peristalsis, received merited attention. The dictum that "cathartics kill the patient with acute perforation" was generally accepted. The fact that restriction in diet, the washing out of the stomach, and water by rectum lessened the danger of the spreading of contamination and infection by peristalsis was established by Ochsner and Murphy. Even the most conservative surgeon began to wake up to the fact that after contamination had passed into peritonitis the most important factor was the peritonitis, and that the so-called early operation was not related in time to when the surgeon saw the patient but to the time when the perforation took place. How well we remember those great debates on appendicitis, when the surgeon, in the heat of argument, said that he "always" did so and so, when he meant "often," and the safety of his patient depended on the fact that he was a better surgeon at the operating table than on the rostrum. When contamination was allowed to pass on to peritonitis, the surgeon had lost his great opportunity and the second dictum was reached: If you must operate in peritonitis for a local lesion, "get in quick and get out quicker," choosing a time when intervention can be safely made rather than to bring a surgical catastrophe on a patient who has only a narrow margin of safety. We learned that the peritoneum had marvelous powers of resistance to infection, and that the surgeon could act only in the capacity of an aid to those natural processes which led to recovery.

It can no longer be said that we are operating for perforation when we do a laparotomy on from the third to the sixth day of a generalized peritonitis. An operation, however, may be wise in order to remove a still active primary focus or secondary deposits of virulent infection, in the hope of limiting the spread of the disease. Acute perforations of the



abdominal viscera, then, so far as the peritoneum is concerned, may be divided into three stages: (1) The stage of contamination, shown by more or less shock and localized pain and tenderness. This is followed by—(2) the stage of reaction; we might well say the fatal stage of reaction, because so large a majority of patients with acute perforations slip by the stage of contamination in which they could have been safely operated on, into (3) the stage of general peritonitis. The apparent improvement which takes place in the period of reaction leads to the belief that the patient is better. Muscular rigidity and tenderness are usually present, but may be absent in the middle-aged, fleshy man whose peritoneum has become anesthetic by reason of fat deposited behind it.

The anatomic situation of the appendix is such that the prospect of the localization of the sepsis and spontaneous recovery are usually good. Recovery, yes, from that particular attack. It is probable that not far from 70 per cent of patients with acute perforation of the appendix might recover from one attack spontaneously, but a death-rate of 30 per cent is a frightful one. No battles of the present war would probably have a death-rate which would exceed it, although they might have a casualty of 90 per cent. In acute perforative appendicitis we have a casualty of 100 per cent, and let us accept as probable a 30 per cent death-rate. But such patients, recovering spontaneously, cannot be said to be well. The majority will have future attacks, in one of which they may not be so fortunate as in the first. I have seen several patients more than sixty years of age with acute intestinal obstruction from bands of adhesions that had their origin in a so-called spontaneous recovery from inflammation of the bowels when a child.

There is a curious relationship between acute perforations of the gallbladder into the free peritoneal cavity and acute perforative appendicitis. I have seen a number of simultaneous perforations of the gallbladder and appendix. In these cases the gallbladder has usually contained stones, the pus has had a strong colon odor, and its bacterial flora has been similar to that in the pus escaping from the appendix. The first case of this kind under my observation resulted most unfortunately as the condition of the appendix escaped attention. The gallbladder had perforated and a beginning septic peritonitis with a great deal of turbid fluid was present. The patient had been ill with acute symptoms for more than seventy-two hours. I, therefore, removed the stones as quickly as possible, drained the gallbladder, and evacuated the fluid contents of the abdomen, made a rapid toilet, and inserted drains. The

atient died forty-eight hours later, when I found that there had been a perforation of the appendix, with an abscess imperfectly walled off, into which a fecal concretion had escaped. Had I discovered the true condition of the appendix at the time of operation there is little doubt that the patient would have recovered. Since that time I have always examined the appendix in cases of acute perforations of the gallbladder, and in a number of instances have seen similar conditions. It would appear that in such cases the infection started in the appendix and was carried through the portal circulation to the gallbladder, already infected and containing stones.

Perforations of the gallbladder into the free peritoneal cavity should and would give the best results of any were it not for the fact that the patient has usually had previous attacks of cholecystitis and believes the present attack is similar to those that he has had before. Early operations, therefore, in such acute perforations of the gallbladder are less liable to be insisted on, and the patient dies, not because of the acuteness or character of the infection, but because of the lateness with which operative procedure is carried out.

Infection reaching the liver by way of the portal circulation is much attenuated by the action of the liver cells, and the escape of septic material from the gallbladder and bile-ducts has a tendency to set up a rather mild peritonitis. On several occasions I have found a perforated gallbladder with escaping gall-stones and beginning peritonitis. In two instances I have removed hundreds of stones by scooping them and the fluid exudate out of the pelvis with the gloved hand, and finally stopped without satisfying myself that I had actually removed all the stones. Such patients, operated on in the first forty-eight hours, have recovered.

The anatomic surroundings of the gallbladder are excellent from the standpoint of protection. The parietal peritoneum, the under surface of the liver, the transverse colon, and the omentum all combine to localize the contaminating material which may escape from the perforation. Free perforation, therefore, while it often takes place, is commonly limited by a rapid protective peritonitis with plastic exudate confined to the immediate vicinity of the gallbladder.

Gall-stones are foreign bodies. While they may remain for long periods of time without evidence of active infection, they are a potential source of focal infection in the production of endocarditis, etc., and when acutely infected, are the common cause of biliary cirrhosis, chronic pancreatitis, etc. We have found a higher percentage of so-called

essential hypertension in connection with gall-stone disease than in any other surgical disorder with which we have come in contact.

The association between the diseases of the gallbladder and biliary tract and the pancreas is shown by the fact that 90 per cent or more of all the patients having acute and chronic diseases of the pancreas that we have operated on have had infected gallbladders and, usually, gall-stones. To all intents and purposes acute fat necrosis and hemorrhagic pancreatitis are the results of perforation of the pancreas and the escape of its secretions. The area of distribution of escaping contents from the pancreas is determined by the fetal pancreas rather than by the adult anatomy. The pancreas in fetal life is entirely surrounded by peritoneum, the posterior layer of which in the adult has become converted into connective tissue, with the formation of the capsule.

The danger of the acute processes of the pancreas, which may be spoken of pictorially as acute perforations, depends almost entirely on whether or not infection co-exists. I have seen aseptic fat necrosis with a large soft pancreas, almost like a pudding in a bag, and acute and subacute pancreatitis in every phase from the earliest, with free peritoneal fluid and most wide-spread fat necrosis, through all the stages to spontaneous recovery, which is a not infrequent termination. This is also true of the pancreatic apoplexies which cause hemorrhagic cysts. I have seen a considerable number of those aseptic, localized collections of blood in and about the pancreas; the patient gives a history, as in fat necrosis, of a most serious, acute illness which gradually subsides and leaves hemorrhagic residue. It is said that activation of the pancreatic juice by the duodenal secretions is necessary to precipitate pancreatitis with fat necrosis or hemorrhage. Infection certainly plays the chief part in determining whether or not the patient will recover. At various times I have opened abscess cavities connected with the pancreas and on several occasions have lifted out a slough which apparently represented the whole of the pancreas, but the recovery of the patient without diabetes or other sequelæ showed that not all the pancreas had been removed.

Deaver has called attention to the possibility of the infection of the pancreas through the lymphatics. The pancreas has five sources of blood supply and lymphatic connections with each. With his usual clarity of vision, Deaver points out that the pancreas has two entirely different secretions, a lipolytic or fat-splitting ferment which saponifies the fat, producing the little areas of lipase that we call fat necrosis, and

trypsin, which acts on the protein tissue, especially the blood-vessels, causing the hemorrhage. Whipple calls attention to a proteose substance which may be produced and cause rapid and fatal toxemia. These observations explain the clinical conditions that we find in the acute forms of pancreatitis. I have been much interested in the recent work of Watts and others in regard to acute pancreatitis and the necessity for direct procedures on the acutely inflamed pancreas. Our experience, however, leads me to take rather a conservative view and to content myself with the anterior abdominal approach to the pancreas and drainage of collections, septic or otherwise, as they occur rather than to anticipate their occurrence by pancreatic incisions. It would appear that, as a result of our early postmortem knowledge and tragic experience with an occasional acute pancreatitis, we have been inclined to underestimate the ability of the tissues concerned to localize or cure a large number of the acute pancreatic inflammations.

Perforations of the duodenum into the free abdominal cavity are the most common of all types of acute perforations, but, fortunately, the duodenal content is more or less sterile, small in quantity, and has a tendency to gravitate into the region of the appendix. For this reason the preoperative diagnosis is often appendicitis, and a high percentage of patients make a spontaneous recovery from that particular attack. Not infrequently the appendix is removed, showing evidences of peritonitis on its surface but without disease of the mucosa, and the true cause of the trouble is not discovered. The patients recover in most instances in spite of the removal of the appendix at an inopportune time, and later they have a recurrence of the duodenal trouble, eventually coming to operation for its cure. In nearly all of our earliest operations for acute perforations of the duodenum a negative exploration of the appendix was first made and the perforation of the duodenum was found during further exploration. It is fortunate, indeed, that an incision one inch to the right of the midline through the rectus muscle enables the surgeon to make a comprehensive examination of the appendix, gallbladder, pancreas, duodenum, and stomach, and gives him ample opportunity to do whatever is necessary without regard to the preoperative diagnosis. We have operated on perforating duodenal ulcers in almost every stage of recovery. The duodenum is unusually well situated, anatomically, for the formation of protective adhesions to the gallbladder, gastrohepatic omentum, transverse colon, etc., which quickly limit the spread

of the contamination, and, after some hours of pain from protective peritonitis, there may be only muscular rigidity and localized pain to mark what was in the beginning a free perforation.

Whether or not a certain condition would be called free perforation, might depend, to a large extent, on whether the operation is done in the first ten or twelve hours, before limiting adhesions are formed, or in the subacute or chronic stage, when the perforation is closed by plastic lymph and the peritonitis has become limited. In a large number of cases of acute perforations in the stage of contamination or localized infection we have operated in the first eight or ten hours, and recovery has nearly always occurred. The results, however, have been much less fortunate when the operations were done between ten and thirty hours: a general spreading septic peritonitis quickly brings many of the patients to a condition in which an operation as a last resort will probably be unsuccessful; a number, however, will, after forty-eight hours, be greatly improved and operation can be done safely. When it is possible to operate on an acute free perforation in the first ten hours, not only will the perforation be closed and the contamination be prevented from passing into a peritoneal infection, but a gastro-enterostomy may be done which means a cure of those conditions that depend on the ulcer and that probably would not have been cured by a mere closure.

What has been said about acute perforations in chronic ulcers of the duodenum applies to ulcers of the pyloric end of the stomach, and, to a considerable extent, to perforation of ulcers on its posterior wall. Perforations of the stomach are much less favorably situated than ulcers of the duodenum in relation to the prospects that the spread of contamination will be quickly limited by neighboring structures. The stomach often has a considerable quantity of contents, at the time of perforation, in a more or less septic condition as contrasted with the rather sterile duodenum, so that there is a greater prospect of an escape of a large amount of septic material into the area of the small intestine instead of gravitating, as from the duodenum, down through Morison's space in front of the right kidney to the iliac fossa. Ulcers of the posterior wall of the stomach frequently become adherent to the pancreas, and along the lesser curvature the gastrohepatic omentum is a good protection. Anterior perforations have a high mortality unless operated on early, for the reasons I have outlined. Fortunately, free perforations of the stomach are the least common of all perforations.

## SUMMARY

1. It may be said that a considerable percentage of free perforations are spontaneously closed, and that the area of peritonitis is limited through natural processes; the death-rate is possibly about 30 per cent, but the 70 per cent of patients who may recover spontaneously from the attack are not cured.

2. An exploration through a longitudinal incision just to the right of the midline gives the surgeon an opportunity to make a careful exploration and to deal with any or all varieties of perforation.

3. Early operation, that is, within the first eight hours, barring accident, means recovery, because the stage of contamination has not yet passed on to infective peritonitis, and measures may still be taken for the permanent cure of the condition which leads to the perforation.

4. Chronic conditions usually precede perforation and give ample warning of their presence before it takes place. While this is accepted, so far as the appendix is concerned, it has not been so generally recognized that gall-stones are foreign bodies which need only infection to lead to the most wide-spread peritonitis, cholangitis, biliary cirrhosis, and pancreatitis.

5. Chronic ulcers of the stomach and duodenum, after a reasonable attempt has been made at medical cure, should be looked on as surgical maladies.

# TORSION OF APPENDICES EPIPLOICÆ\*

V. C. HUNT

## INTRODUCTION

The appendices epiploicæ appear along the whole of the large intestine except the rectum, where they terminate quite abruptly. They consist of little processes or pouches of peritoneum; no other part of the intestinal wall enters into their formation, the space or sacculum being filled with a variable amount of fat, usually considerable in obese persons. Their shape and size are variable, frequently dependent on their fat content. They are often more or less flattened, but may be quite cylindric. When flat, they may be lobulated. Their size is variable along the course of the large bowel and in different persons, the smallest occurring along each side of the mesentery of the appendix vermiformis. The development is moderate on the ascending and descending colon, and the greatest size is usually on the transverse colon and sigmoid flexure. Their length varies from 0.5 to 5 cm., but they have been reported 15 cm. in length (Linkenheld). As a rule, but one artery and one vein enter the base of the appendix epiploica. The appendices epiploicæ occur quite evenly in two rows, their line of origin often being quite close to the anterior and posterior inferior longitudinal muscle bands.

Harrigan quotes Robinson in saying that the physiologic function of appendices epiploicæ is not protective and defensive, like the great omentum, as they are simple in structure and present no evidence of specialized function. It is Robinson's belief that these appendices epiploicæ are concerned with the movement of fluids in the large intestine; however, no definite evidence of their true function has been brought to light.

The pathologic changes incident to the appendices epiploicæ are usually those attending mechanical interference with the blood supply.

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either by torsion or direct pressure, torsion being perhaps the only cause within the abdomen that is not limited to the abdominal cavity. A considerable number of cases have been reported in which torsion of an appendix epiploica has occurred in a hernial sac, this being the most common site for mechanical interference by direct pressure and strangulation without torsion; however, torsion occurs here also. In either event the interference with the circulation may be suddenly complete or gradually progressive. Fat necrosis is the chief degenerative change, there frequently being considerable inflammatory reaction, particularly in those cases of hernia as is manifested by the adhesions which frequently close off the neck of the sac, and the presence of serum (Serve, Kendirdjy, and Sejournet, and Schweinburg cases). Subperitoneal hemorrhagic effusions occur (Lorenz, Zoeppritz, Mohr, Schweinburg, and Linkenheld cases) and at times only small ecchymotic areas with dark discoloration of the appendix epiploica have been seen. In the abdominal cavity these same changes take place, with torsion, and several appendices epiploicæ may adhere over the one in which torsion has occurred, in a way suggesting protection. The affected appendix epiploica then becomes encysted, and fat necrosis and saponification take place until the cyst contains but an oily, straw-colored fluid, as was seen in Case A43849.

Since all cases of torsion of an appendix epiploica present acute pathologic processes, characterized by subperitoneal hemorrhagic effusion, fat necrosis, gangrene, etc., infection of the appendix epiploica by direct microbic invasion from the lumen of the bowel because of interrupted continuity, as is seen in diverticulitis of the colon, seems a very probable etiologic factor. Many authors have noted the frequent presence of diverticula in relation to the appendices epiploicæ. Telling says: "Bland Sutton has stated and illustrated by diagrams that this fat is directly continuous with the subserous fat, and if there is any tendency to the formation of diverticula, it will be readily seen that the soft fatty tissue of the appendices epiploicæ form points of lowered resistance." McGrath states that the relationship between diverticula and appendices epiploicæ seems to be due to the fact that these fatty masses are situated either directly on or close to the points where the larger vessels enter the intestinal wall. Greaves reports a case in which there was an acute inflammatory process in two appendices epiploicæ of the pelvic colon. They were nodular, black in color, and each one contained a fecal concretion, but no communication with the lumen of



the bowel could be found. However, while torsion of these appendices epiploicæ had not occurred, the inflammatory process was undoubtedly due to microbic invasion by way of a diverticulum. Erdmann found in most of his cases of acute diverticulitis of the colon, involvement of one or more appendices epiploicæ which were usually very hard and injected or hemorrhagic and becoming gangrenous.

In some of the cases of diverticulitis of the colon with tumor formation seen in the Mayo Clinic the appendices epiploicæ have been found involved in the inflammatory process in a way suggesting protection to perforation of the diverticula. Virchow's case, in which colon bacilli were cultivated from the center of a foreign body found in the peritoneal cavity, as the sole cause of a peritonitis, adds evidence to the infection theory. Diverticulitis was not found in any of the cases of torsion of appendices epiploicæ reported in the literature, nor was it demonstrated in our cases, yet it seems that infection may prove to be the etiologic factor in the production of torsion and of inflammation in appendices epiploicæ.

Torsion intra-abdominally of an appendix epiploica may suddenly deprive it of its circulation, and with no protection from the omentum or neighboring appendices epiploicæ necrosis of the narrow pedicle occurs so rapidly that it drops off and remains in the peritoneal cavity as a free body, encysted by its peritoneal coat. Such fatty bodies have been found in 4 cadavers (Littre, Laveran, Cruveilhier, and Virchow) and in 7 instances at operation (Schede, Neri, Riedel 4, and Case A210428). Of those found in the cadavers, one contained a stone and in two the foreign bodies were fibrocartilaginous. The case of Virchow showed an atrophied appendix epiploica as a possible source of the foreign body. The foreign bodies found at operation retained their fatty composition in all cases except one (Schede), in which calcification of the body had occurred. These foreign bodies varied in size from the size of a pea to a hen's egg. Colon bacilli were isolated from one of the bodies (Riedel's fourth case) as the source of a fatal peritonitis. In four of these cases operation was done for acute or subacute conditions, and nothing else was found to explain the symptoms.

#### DISCUSSION OF CASES REPORTED IN THE LITERATURE

The literature contains records of 42 cases which have accumulated under the combined titles of "torsion and inflammation of appendices epiploicæ." It seems advisable to divide these cases into their true

classifications, rather than into one large group, according to the pathologic condition presented.

Nineteen were cases of true torsion of an appendix epiploica, intra-abdominal in 9 cases and within a hernial sac in 10. One case of intra-abdominal torsion was a finding at necropsy; the remainder were seen at operation and each presented an acute process. The intra-abdominal cases possessed symptoms of acute surgical conditions in which the diagnosis of acute appendicitis was made in three instances, intestinal obstruction in two, gall-stones in one, ovarian disease in one, and appendicitis and gallbladder disease in one. There were no pathologic findings to explain the acute symptoms except the torsion of the appendices epiploicæ.

The 10 patients with hernias in whom torsion of an appendix epiploica had occurred all had acute symptoms on which the diagnosis of strangulation or incarceration of the hernial contents was made. In 12 cases of hernia in which the symptoms were acute there were from one to three strangulated or incarcerated appendices epiploicæ, showing the inflammatory reaction and fat necrosis attending mechanical interference with blood supply without torsion of the pedicles.

The literature contains accounts of 11 cases of foreign body in the peritoneal cavity which are assumed to have been the results of torsion of appendices epiploicæ, and while evidence in its support is presented in but one case (Virchow) in which there was found an atrophied appendix epiploica, the possible source of the foreign body, that assumption is probably correct. However, in the absence of facts establishing these cases as true torsion of appendices epiploicæ it seems they should not be classified in that group.

One case (Patel) from the report is a true case of diverticulitis for which the diagnosis is easily mistaken.

Excluding the last 12 cases, the literature contains but 30 cases in which there has been mechanical interference with the blood supply of an appendix epiploica, and in 19 of these it was by torsion. The symptoms in each of these 30 cases were of sufficient severity to require urgent surgical interference.

Several theories regarding the cause of intra-abdominal torsion of appendices epiploicæ have been advanced. Morestin states that for torsion to occur it is necessary that these fatty appendages should be abnormally long and large. Ebner quotes Payr's theory of the difference of length of artery and vein, the vein being the longer by reason of its winding course. In congestion, particularly in stasis with engorgement

of the veins, this difference of length may furnish the tendency to the twisting of the pedicle.

Zoeppritz's patient had an adhesion to the omentum which, on sudden movement in the abdomen, due to a quick turn of the patient, may have been responsible for the torsion of the appendix epiploica. Zoeppritz quotes Küstner, Mickwitz, and Cario as regards external causes, such as peristalsis and variations in the filling of the abdominal organs, contraction of the abdominal muscles, and the effect of abdominal pressure, being sufficient to cause torsion of intraperitoneal bodies.

Torsion of an intrahernial appendix epiploica is explained by Ebner in a certain case by its twisting on its exit into the hernial ring at the moment of coughing, similar to the spiral twisting of a cloth used in cleaning a lamp chimney; the tip of the appendix epiploica follows along the wall of the sac, and its base or pedicle remains more or less fixed. In some instances the appendices epiploicæ are carried into the hernial sac with omentum and torsion is produced.

#### DISCUSSION OF CASES FROM THE MAYO CLINIC

To the cases reported in the literature I desire to add 11 cases which have been under observation in the Mayo Clinic in the past ten years. Seven of these cases are true torsion of the appendix epiploica, 1 is of doubtful torsion, acting as a band producing intestinal obstruction, 2 are of incarceration in a left inguinal hernia, and 1 is of a foreign body in the peritoneal cavity with unproved origin from an appendix epiploica. Four of the cases of torsion presented acute symptoms, for which operation was done, and in the remaining 3 cases the torsion was probably symptomless, as it was found in the course of abdominal operations for other pathologic conditions. The cases in which there was incarceration in a hernial sac presented symptoms of incarceration of the hernial contents. The foreign body was found in the course of an operation for postoperative hernia, and the appendix epiploica, producing the obstruction of the sigmoid, manifested symptoms of chronic intestinal obstruction.

It may be seen from the histories of cases from the literature and those included in our series that intra-abdominal torsion produces symptoms, acute in various degrees, simulating those of gall-stone colic, acute appendicitis, intestinal obstruction, etc., the pain not necessarily occurring directly over the seat of the lesion, for while the sigmoid has been the portion of the bowel most frequently affected, the pain has in many instances

been in the right abdomen. In the combined series of cases (40) in which mechanical interference with the blood supply to the appendix epiploica had occurred, the origin of the appendix was in the sigmoid in 28 instances, in the cecum in 6, in the transverse colon in 1, and not stated in 5. Left inguinal hernias are more apt to contain epiploic tags because of the close proximity of the sigmoid, with its long mesentery, to the internal ring of a left hernia. In the 24 cases of torsion or strangulation of the appendix epiploica in a hernial sac it was found in a left inguinal hernia in 17 instances, in a right inguinal hernia in 5, and in a left femoral hernia in 2.

The amount of torsion of the appendices epiploica has varied from one turn through 180 degrees (Zoeppritz) to 10 half-turns (Adler). It has been stated (Briggs) that torsion of appendices epiploicæ usually occurs in persons more or less obese during middle life or later. In 24 of the 26 cases of torsion in which the age was given the youngest patient was twenty years and the oldest seventy-two, an average age of forty-five years; 5 each in the third and fourth decades, 4 in each of the fifth, sixth, and seventh, and 2 in the eighth decade.

Intra-abdominal torsion occurred 11 times in the male and 5 times in the female. Within a hernial sac it occurred 6 times in the male and 4 times in the female, the males comprising 65 per cent of the entire series of torsion.

#### ABSTRACTS OF REPORTS OF CASES IN THE LITERATURE

##### *Appendices Epiploicæ as Foreign Bodies*

CASE 1.—In 1703 Littré, during the dissection of a cadaver, found in the abdomen a free, hard, oval body, one inch long. In its center was a round white stone, the size of a pea.

CASE 2.—In Virchow's case the patient died of peritonitis. A hard calcified foreign body was found in the abdominal cavity, the possible source being an atrophied appendix epiploica of the vermiform appendix.

CASE 3.—In 1894 Schede reported a patient who had symptoms of ileus, and at operation a free body, hard and the size of an egg, was removed from the pelvis and found to be a calcified appendix epiploica.

CASE 4.—In 1894 Cruveilhier, at necropsy after death of unknown cause, found a large foreign body with white, smooth surface, very hard and perfectly free in the abdomen.

CASE 5.—In 1895 Laveran at necropsy found a mass of twelve fibro-cartilaginous bodies in the abdomen.

CASE 6.—In 1904 Neri found at operation several foreign bodies composed of fat within a connective-tissue envelop.

CASE 7.—In one of Riedel's group of cases, reported in 1905, the patient had attacks of pain simulating gall-stone colic and a diagnosis of adhesions about the gallbladder was made. At operation two foreign bodies, almost as large as a cherry, were removed. The pains recurred and three years later the patient committed suicide. The necropsy revealed two more foreign bodies free in the peritoneal cavity.

CASE 8 (Riedel).—The patient was a male, twenty-five years of age, who, four years previously, had been operated on for an appendical abscess, with removal of the distal end of a gangrenous appendix. He had three indefinite attacks of pain with abscess formation in the umbilical region. Operation disclosed two small, yellow, round foreign bodies.

CASE 9 (Riedel).—The patient was a male, thirty-two years of age, whose symptoms were those of gall-stone colic with jaundice. At operation the gallbladder contained no stones. The omentum was adherent to the liver, and the transverse colon and two foreign bodies were slightly adherent to it. They were round and calcareous. A number of appendices epiploicæ were hanging by a mere thread from the transverse colon.

CASE 10 (Riedel).—The patient, a female forty-one years of age, had been sick for eight days and presented the symptoms of peritonitis. At operation there were marked signs of peritonitis. A crescent-shaped appendix epiploica, attached to the descending colon, with a flat, gray foreign body lying free between it and the abdominal wall, seemed to be the sole cause of the peritonitis. The appendix epiploica was not twisted. Colon bacilli were found in the foreign body, which was composed of fat. The patient died on the third day after operation, and necropsy did not disclose any other cause for the peritonitis.

CASE 11 (Riedel).—The patient had been vomiting for fourteen days, the vomitus at last becoming fecal. A diagnosis of intestinal obstruction was made. At operation a foreign body the size of a bean lay free in the peritoneal cavity. The parent appendix epiploica seemed to spring from the cecum and was adherent to a coil of small intestine in such a way as to act as a constricting band, the small intestine being greatly distended. The foreign body was composed of fat and Riedel considered it a part of the appendix epiploica from which it had become separated by torsion.

#### *Intra-abdominal Torsion of Appendices Epiploicæ*

CASE 12.—In a case of Tomellini's, of a man dead of cardiac paralysis, necropsy revealed that the appendices epiploicæ of the transverse colon and sigmoid were straighter than usual. A flattened appendix epip-

loica was found the same color as the others, and bound to the mass by a thin pedicle. This pedicle had undergone a true torsion around its long axis.

**CASE 13 (Riedel).**—This patient was a man forty years of age, who, three days before admission, complained of severe abdominal pain, vomiting, etc., and presented the picture of intestinal obstruction. At operation there was free fluid in the abdomen, the jejunum was greatly dilated, the ileum less so. Arising from the left wall of the cecum, an appendix epiploica stretched across the ileum and was adherent by its twisted middle portion to the mesentery of a coil of small intestine. The ileum was greatly contracted by the appendix epiploica, acting as an obstructing band, and was relieved by the removal of the appendage. Enterostomy was done to relieve the obstruction. The patient died on the following day and necropsy disclosed peritonitis.

**CASE 14.**—Briggs, in 1908, reported the case of a male, thirty-five years of age, without a history of previous abdominal complaint. He had had a sudden attack of right lower abdominal pain, which gradually subsided, but increased later in the day. The pulse and temperature were normal. A tumor was palpable over the tender region of the appendix. On the fifth day, with the patient's temperature 100° F., operation was performed. Presenting in the incision was a tumor 1½ inches long and 1 inch wide, having the appearance of a hematoma with a peritoneal envelop. It was adherent to the cecum by a narrow twisted pedicle. The appendix vermiformis, though normal, was removed. The tumor was an appendix epiploica with a twisted pedicle.

**CASE 15.**—Zoeppritz reported a case in 1909 in which the patient was a male, twenty years of age. For three weeks he had burning pains in the right epigastrium, extending toward the midline. Before examination he had acute epigastric pain and there was tenderness at McBurney's point. The diagnosis lay between acute appendicitis and acute cholecystitis. The appendix vermiformis appeared in the incision and did not seem to be the cause of the acute symptoms. Upon lengthening the incision a brownish, bluish-red mass the size of a plum appeared in the wound, from the center of which extended a slightly thickened band of omentum. The removed tumor was an appendix epiploica of the beginning of the transverse colon twisted 180 degrees. When the omentum was loosened there was no tendency to untwist.

**CASE 16.**—In Ebner's case, reported in 1909, the patient was a male, sixty-five years of age, who had had a right inguinal hernia for fifteen years and a left inguinal hernia for a shorter length of time. Seven days before examination, after lifting a heavy load, he felt severe pain in the right side of the abdomen. The hernia could be reduced, but three days later there was much hypogastric distention and tenderness, with moderate increase in temperature for two days. Retention of

feces and flatus with vomiting occurred, a diagnosis of intestinal paralysis was made, and immediate operation performed. There was a small amount of clear, bloody fluid in the abdominal cavity, and a pedunculated fat tag, 15 cm. long, arising from the sigmoid and extending from the left inguinal region over to the right side by a thin pedicle, was twisted through 180 degrees. This proved to be an appendix epiploica. As a result of the torsion congestion and extravasation of blood had occurred in the fat tag. After operation the symptoms of intestinal paralysis were progressive and the patient died on the seventh day. The author explains the intestinal paralysis as being due to the coagulation processes in the mesenteric vessels following torsion of the appendix epiploica.

CASE 17.—Pochhammer, in 1910, reported a case of a patient, a male thirty-four years of age, who had during the past eighteen years repeated attacks of pain in the right lower abdomen which had been diagnosed as appendicitis. He had a similar attack just before admission to the hospital, with no nausea or vomiting. From the history and examination the diagnosis of appendicitis was made and operation performed. In the pelvis was found a hard, fatty tumor the size of a hen's egg, bluish-black in color, and its central portion was infiltrated with blood. It was evidently an appendix epiploica which had become enlarged from fatty infiltration and the pedicle had become twisted. The vermiform appendix was shrunken and showed no evidence of inflammation, but was removed.

CASE 18.—Morestin reported a case in 1912 in which the patient was a female thirty years of age, who ten days before examination experienced sudden severe left abdominal pain with nausea and moderate temperature for twenty-four hours. Four days after the onset a tender mass the size of a large egg, separate from the uterus, could be felt in the left side of the pelvis. A diagnosis of left tubo-ovarian disease was made and operation performed, at which time atrophy of the uterus and its appendages was found. A mass in the left side of the pelvis in the middle of a few blood-clots and recent adhesions, purplish in color, with some attachment to the uterus and broad ligament, had its origin in the sigmoid by a narrow pedicle, twisted upon itself, and proved to be an appendix epiploica. The patient's convalescence was uneventful.

CASE 19.—Kimpton reported a case in 1915 of a patient, an obese male, forty-two years of age, who had had acute pain in the right lower quadrant of the abdomen, with nausea. He had had one or two previous similar attacks. The lower right quadrant of the abdomen was rigid and tender; the pulse and temperature were normal. A diagnosis of acute appendicitis was made, and at operation a black appendage of fat presented in the region of the appendix vermiformis which was a twisted appendix epiploica. It was removed and, although the vermiform ap-

pendix was normal, appendectomy was done. Further abdominal exploration was negative. The twisted appendix epiploica was hemorrhagic and necrotic. The convalescence was uneventful.

CASE 20.—Harrigan, in 1917, reported a patient, a male, twenty-nine years of age, who two days before examination had sudden severe pain in the right lower quadrant of the abdomen, with no radiation, which became progressively worse in spite of the use of opiates. Physical examination was negative except for a slight rigidity and tenderness over McBurney's point. The temperature was 100° F., pulse 98, and respiration 24. A diagnosis of acute appendicitis was made and immediate operation performed. The vermiform appendix was not inflamed, and general exploration of the abdomen was negative except in the sigmoid, where an appendix epiploica presented evidence of acute inflammation, the pedicle being twisted. The appendix epiploica was removed by ligation of its pedicle and the vermiform appendix removed, with the patient's complete recovery.

#### *Intrahernial Torsion of Appendices Epiploicæ*

CASE 21 (Riedel).—The patient was a female, twenty years of age, who had had a left reducible femoral hernia for ten years and an irreducible right femoral hernia for a few months. On the day before examination the patient had violent abdominal pain with tenderness of the left femoral hernia. At operation the next day a fatty structure, 1 cm. by 5 mm., was found suspended from the wall of the sac by a thin pedicle of fibrin. The case seems to have been one of torsion.

CASE 22 (Riedel).—The patient was a female fifty-six years of age. For two years she had had a right inguinal and a left femoral hernia. Two days before admission to the hospital the patient suffered with severe pain in the left groin, and the femoral hernia was then an irreducible tumor. Immediate operation showed an appendix epiploica twisted once on its axis and adherent by its distal extremity in the hernial sac. Necrosis had already begun. The pedicle was ligated and the appendix epiploica removed, with radical cure of the hernia and recovery.

CASE 23.—Servé, in 1906, reported the case of a male patient who had had a left inguinal hernia for many years in which, two days before examination, he experienced a violent pain following a severe muscular effort. The scrotum was swollen, and at operation a few drops of fluid escaped from the hernial sac, which revealed as the content an appendix epiploica 10 cm. long, completely twisted on itself. This was removed and radical cure of the hernia was followed by recovery.

CASE 24.—Muscatello, in 1906, reported a case of a patient, a male, thirty-eight years of age, who had experienced a sudden pain in the left



inguinal region six months previously, the pain disappearing for a month. He had a left inguinal hernia extending into the scrotum which at operation contained omentum in the sac and an appendix epiploica adherent to the posterior border of the neck of the sac and twisted on itself. The torsion occurred 5 mm. from the insertion of the appendix epiploica on the colon. Removal of the appendix epiploica and radical cure of the hernia were followed by recovery.

CASE 25.—In 1907 Mohr reported a case of a patient, a male, sixty-two years of age, who had had for the past three to four years a reducible tumor of the left inguinal region which, ten days before examination, became irreducible. On the diagnosis of strangulated hernia operation was performed, and in the hernial sac an appendix epiploica was found which presented hemorrhagic infiltration. The tips of two other appendices epiploicæ presented in the sac, springing from the sigmoid, and were in a state of torsion, with gangrene imminent. They were removed; the patient recovered.

CASE 26.—Lorenz reported a case in 1906 in which the patient, a female, thirty-three years of age, had a right inguinal hernia, much abdominal pain, and symptoms of intestinal obstruction. Operation revealed in the hernial sac, among loops of intestine and inserted mesially to the neck of the sac, a narrow, tense, pseudo-ligament about 6 cm. long, and around which an appendix epiploica, arising from the colon, had become twisted and strangulated, torsion being through 360 degrees. The immediate visceral and parietal peritoneum was covered with fresh fibrin and the twisted appendix epiploica showed subperitoneal effusions of blood and gangrene of the pedicle at the point of strangulation. The band and appendix epiploica were resected with good recovery.

CASE 27.—Krüger reported, in 1907, the case of a patient, a male, fifty-six years of age, who had had an attack of pain in the right groin twenty years before which disappeared after a few weeks, to recur two years previous to admission to the hospital and again four days previously. The pain radiated from the urethra to the umbilicus. There was a firm mass in the right inguinal region, which, at operation, proved to be an appendix epiploica 4 cm. by 1.5 cm., and springing from the cecum by a short pedicle which had passed through the inguinal canal and become twisted in the hernial sac, giving rise to the inflammatory symptoms. The appendix epiploica was removed, with radical cure of the hernia.

CASE 28.—In 1908 Adler reported a case in which the patient, a robust woman, seventy-two years of age, had had a left reducible inguinal hernia for twenty years. The day before admission to the hospital the hernia became irreducible. An operation was done immediately, and a cord-like mass lying in an edematous sac was found. The

mass was of omental tissue, which ended below in an enlargement the size of a chestnut. The cord was twisted on itself and contained ten half-turns, the whole lying quite free in the hernial sac. On following the cord down it was found to have its origin from the large intestine and proved to be an elongated twisted appendix epiploica. The hernia was repaired and there was an uninterrupted recovery.

CASE 29.—In 1908 Linkenheld reported the case of a patient, a fleshy man sixty-four years of age, in whom eight days previously a painful, irreducible swelling had appeared in the right inguinal region. A diagnosis of strangulated omental hernia was made. At operation the hernial contents were found to consist of omentum and a twisted connective-tissue cord extending up into the abdominal cavity. This was ligated and the omentum removed, with radical cure of the hernia. The patient died on the sixth day from gastric hemorrhage, and necropsy showed multiple ulcers of the stomach; also six long, thick and fat appendices epiploicæ of the sigmoid were found with the tied pedicle of the cord in the hernial sac.

CASE 30.—In 1910 Kendirdjy reported a case of a patient, a male, forty-three years of age, who had had a left inguinal hernia for twelve years. Two weeks before examination severe pain in the hernia and swelling were noted. Two days before examination symptoms of intestinal obstruction appeared and the skin overlying the hernia was inflamed and tender. When the hernial sac was opened, some yellow fluid escaped and a yellow, fatty mass, presenting ecchymotic areas, formed its contents. This was attached to the sigmoid by a pedicle, in which torsion one and one-half times had occurred. The pedicle was ligated, with radical cure of the hernia and recovery.

#### *Intrahernial Strangulation or Incarceration of Appendices Epiploicæ*

CASE 31.—In 1906 von Bruns reported the case of a patient, a female, fifty-five years of age, who had had a left inguinal hernia for four years. It became suddenly painful, swollen, and irreducible, the overlying skin becoming red and edematous. At operation a small amount of fluid escaped and revealed a gangrenous strangulated appendix epiploica, which was removed, and good recovery occurred.

CASE 32.—Muscatello reported a case in 1906 of a patient, a female, fifty-six years of age, who was suddenly attacked by violent femoro-inguinal pain on the left side, radiating all over the abdomen, and in which the diagnosis of strangulated femoral hernia was made. Operation under local anesthesia allowed the escape of clear yellow fluid and the exposure of two appendices epiploicæ, measuring 2 and 1.5 cm. respectively, attached by narrow pedicles to the sigmoid. The appendices epiploicæ were removed and the sac resected, with a radical cure of the hernia and recovery of the patient.

**CASE 33.**—In 1906 Schweinburg reported the case of a patient, a male, forty-five years of age, who had had a reducible left inguinal hernia for years. Six days before admission to the hospital the hernia became irreducible and painful and tender. At operation the hernial sac contained odorless fluid and three appendices epiploicæ, which were thickened and hemorrhagic, and, on being drawn down, were found to have their origin from the sigmoid. They were removed, with radical cure of the hernia and recovery.

**CASE 34.**—Verga reported a case in 1907 of a patient, a female, forty-six years of age, who developed a right inguinal hernia at twenty-three years of age and a left inguinal hernia at twenty-six, both of which remained reducible until eight days before examination, when the left hernia could not be reduced. There was some pain from it radiating to the hypogastrium, but no nausea, vomiting, or evidence of intestinal obstruction. In the left inguinal region there was a mass the size of an almond which was tender. On the diagnosis of an irreducible hernia operation was performed Nov. 4, 1906, at which time two appendices epiploicæ were found strangulated in the hernial sac, showing vascular engorgement and several hemorrhagic points. They originated from the sigmoid. They were ligated and cut off and the hernia repaired, with good recovery.

**CASE 35.**—Vulliet reported a case in 1907 of a patient, a male, sixty-two years of age, who had had a double inguinal hernia for twenty years. There was severe pain in the left inguinal region three days before admission to the hospital. At operation the left hernial sac contained two appendices epiploicæ with thin pedicles extending to the sigmoid. Removal of the appendices epiploicæ and radical cure of the hernia were followed by recovery.

**CASE 36.**—In 1907 Smoler reported a case of a patient, a male, aged thirty-seven years, who, on admission to the hospital, complained of nausea and weakness and who had noticed two days previously that a right inguinal hernia was no longer reducible. On examination the patient was found in a state of moderate shock and an operation was done immediately. The hernial sac was thick and contained bluish-red, discolored omentum, with incipient necrosis due to torsion of 360 degrees of that part of the omentum. By the side of the omental mass, at the median side of the hernial aperture, a structure as thick as the finger and 2 cm. long presented, which proved to be an appendix epiploica of the sigmoid. The omentum and appendix epiploica were removed, with death of the patient on the fifth day.

**CASE 37.**—In 1908 Linkenheld reported the case of a female, fifty-seven years of age, in whom there appeared, eight days before examination, a swelling in the right inguinal region which caused severe pain. The swelling was firm and tender. At operation, strangulated in the

neck of the hernial sac was a piece of fat the size of a hazel-nut. After freeing the adhesions the fat tag could be withdrawn. It exhibited a distinct constriction and proved to be an appendix epiploica, probably of cecal origin.

**CASE 38 (Linkenheld).**—The patient, a male, seventy-one years of age, had had a left inguinal hernia for a year, in which, two days before admission, pain, swelling, and reddening of the skin occurred, with no symptoms of obstruction. The hernia was tender to pressure. At operation the contents of the hernial sac consisted of three appendices epiploicæ, one the thickness of the finger and the other two the thickness of a lead-pencil. They were swollen, reddened, and infiltrated with blood, being strangulated at their upper ends. Two days later the patient died from ruptured aneurysm, as revealed at necropsy, which also showed enlarged appendices epiploicæ of the descending colon and sigmoid.

**CASE 39.**—Tisserand, in 1908, presented a report of a patient, a male, thirty-six years of age, who had had a left inguinal hernia all his life which the past year had at times been painful and irreducible. Sixteen hours before examination he had had a violent colic in the hernia, with some nausea, but no vomiting. Immediate operation disclosed two appendices epiploicæ in the hernial sac with some free fluid. One appendix epiploica was not strangulated, but the other was swollen, ecchymotic, and in the process of becoming gangrenous from strangulation. Its origin was probably from the cecum. These appendices epiploicæ were removed, the hernia repaired, and the patient had an uneventful convalescence.

**CASE 40.**—Truffi, in 1908, reported the case of a patient, a female, forty-five years of age, who about a year previously noticed a swelling in the left groin which appeared suddenly and remained for a week. Eight days before examination the swelling recurred. It was painful to pressure; the pain gradually subsided, but the swelling persisted. On admission to the Clinic it was the size of a hen's egg and was not reducible. A diagnosis of irreducible hernia was made, and at operation the sac was found to contain a small amount of dark-red liquid and two club-shaped fat bodies which were covered with numerous hemorrhagic points, and proved to be appendices epiploicæ strangulated at the neck of the sac. They probably originated from the sigmoid. They were removed and the hernia repaired.

**CASE 41 (Truffi).**—The patient, a male, seventy-five years of age, had had a double inguinal hernia for forty years, the left disappearing of its own accord and the right by operation two years previously. About two months before examination he had had severe pain in the left inguinal region, with recurrence of the left inguinal hernia, which was irreducible, with a sense of pressure and pain. Operation was ad-

vised. In the sac of the hernia were found two appendices epiploicae with strangulation of their pedicles in the neck of the sac. Convalescence was uneventful.

CASE 42.—In 1912 Patel reported the case of a patient, a male, forty-five years of age, who had had a left inguinal hernia for twenty years. Eight days before admission to the hospital the hernia became irreducible and painful. The overlying skin was red and edematous, as was the scrotum. The symptoms continued, and a diagnosis of strangulated hernia was made. An incision of the hernial sac allowed the escape of a seropurulent liquid. An appendix epiploica was strangulated in the hernial sac. The tag was ligated and removed. The end of the pedicle had a lumen communicating with the lumen of the large intestine, which proved to be a diverticulum into the appendix epiploica.

#### CASES FROM THE MAYO CLINIC

##### *True Intra-abdominal Torsion of Appendices Epiploicae*

CASE 43 (A8716).—R. A. K., a male, fifty-eight years of age, was admitted to the Clinic April 10, 1908. The previous history was negative except for severe constipation for years. Two weeks previously pain was noticed on defecation; there was some mucus in the stool, but no blood. The pain continued and was aggravated by enemas. There were no other subjective symptoms. A mass could be felt per rectum, and the diagnosis of a tumor of the sigmoid was made.

Operation was performed April 15, 1908, and an appendix epiploica with a twisted pedicle was found. The pedicle had its origin about five inches above the rectum, and the appendix epiploica had dropped to the bottom of the pouch of Douglas, forming a cystic and adherent mass the size of an orange. The appendix epiploica was removed, with recovery of the patient.

CASE 44 (A6851).—A. Mc., a carpenter, forty-three years of age, was admitted to the Clinic April 26, 1910. Less than a year previously he had had an appendectomy with negative exploration of the gall-bladder. The history of the present complaint was pain in the right side of the abdomen opposite the umbilicus for four years, very severe at the onset, the patient being in bed four days at that time with diarrhea and vomiting. The symptoms recurred every two or three months. Appendectomy was performed less than a year previous to examination, with recurrence of a similar attack two months later. During the past six months the attacks had been more frequent, the pain lasting from five to six hours and always accompanied by diarrhea. There was no disturbance of the bowels between attacks, and no radiation of pain. At times there were spells of indigestion, but never any symptoms of organic disease of the stomach or duodenum. Seven days before admission the patient had had a severe attack of left lower abdominal

pain accompanied by vomiting of four hours' duration, and requiring morphin to control. The general physical examination, urinalysis, x-ray examination of the kidneys, ureter, and bladder, and cystoscopic examination were all negative.

May 3, 1910, exploration was made of the stomach, gallbladder, and left ureter. These proved negative, but a twisted appendix epiploica of the sigmoid, with its circulation completely cut off, was found. There also were adhesions of the terminal four inches of ileum to the lateral abdominal wall; these were divided and the appendix epiploica removed. Within the next four months there were several recurrent attacks of pain; the further history of the case is not known.

CASE 45 (A38941).—Mrs. F. L., aged twenty-nine years, was admitted to the Clinic June 14, 1910. For seven years the patient had had attacks of moderate pain in the right lower abdomen, usually of only a few minutes' duration, and never severe enough to keep her from her work, but at times they had been of the nature of a dull ache for a day at a time. During the two months preceding examination there had been moderate digestive disturbance, but never any acute attacks of pain. A diagnosis of chronic appendicitis and cholecystitis was made.

June 20, 1910, operation was performed and chronic adherent appendix, and an appendix epiploica, the size of a small pecan, with a twisted pedicle, were found and removed. Exploration of the gallbladder and stomach was negative.

CASE 46 (A69658).—Mrs. J. J., aged sixty-three years, was admitted to the Clinic June 24, 1912. The patient had been perfectly well until three months previously, at which time she was confined to bed with burning pain and cramps in the left lower abdomen and much localized tenderness. This had been more or less constant, with the pain radiating around to the sacral region. Constipation, walking, and working aggravated the trouble. Physical examination disclosed tenderness in the left abdomen, moderate edema of the legs, due to large varicose veins, and complete uterine prolapsus with rectocele and cystocele. X-ray of the kidneys, ureters, and bladder was negative.

July 3, 1912, because of the complaint referred to the left lower abdomen, an abdominal operation was done. A calcareous appendix epiploica of the sigmoid with a twisted pedicle was found. Other exploration of the abdomen was negative. The appendix epiploica was removed, and a Kocher abdominal operation done for the prolapsus.

CASE 47 (A162332).—Mrs. J. B., seventy years of age, was admitted to the Clinic June 10, 1916. Three years previously the patient began having occasional uterine bleeding for a few days at a time, which continued for a year. For two years the discharge had been scant, and for six months watery in character. The uterus was enlarged. The menopause had occurred when she was forty-eight years of age.

June 14, 1916, total abdominal hysterectomy with removal of both ovaries and tubes was done for carcinoma of the body of the uterus and multiple fibroids. Two appendices epiploicæ with twisted pedicle, making a mass the size of the thumb, were found and removed. These were reported by the pathologist to be hemorrhagic. There had been no history of a recent acute abdominal complaint.

CASE 48 (A181741).—P. B., a male, aged thirty-seven years, was first seen January, 1917. One month previously the patient had had sudden severe pain in the left lower abdomen, with much localized tenderness, which had partially subsided a few days before examination. The patient was a large man who had lost 20 pounds in weight since the onset of the complaint. The urinalysis, blood, and x-ray examination of the colon were negative. A diagnosis was made of probable diverticulitis.

Operation was performed Jan. 5, 1917. A general exploration of the abdomen showed the small intestine and the gallbladder to be normal, the appendix small, short, and normal, and the sigmoid markedly thickened, with one epiploic tag about  $1\frac{1}{4}$  inches long and  $\frac{3}{4}$  inch wide, twisted on its pedicle. Fat necrosis had occurred and the appendix epiploica had become adherent to surrounding epiploic tags. The tags which were involved in the inflammatory mass and the one undergoing necrosis were removed and their stumps ligated. There was no evidence of diverticulitis.

CASE 49 (A43849).—Mrs. E. A. H., fifty-one years of age, was admitted to the Clinic Nov. 7, 1917. The patient presented herself for examination because of a troublesome watery vaginal discharge for which hysterectomy was advised. There were no symptoms of an acute abdominal process. She had passed the menopause at thirty-six years of age.

Nov. 12, 1917, total abdominal hysterectomy with removal of both ovaries and tubes, for chronic metritis of the precancerous type, was done. An appendix epiploica of the sigmoid appeared in the wound. It was a round body, about 2 cm. in diameter, and was twisted on its pedicle. It had become encysted and contained a clear, straw-colored fluid and oil. There was nothing in the patient's history to indicate that it had produced subjective symptoms.

#### *Appendices Epiploicæ as Foreign Bodies*

CASE 50 (A210428).—Mrs. C. B., aged forty-two years, was examined Oct. 8, 1917. The patient, who was very obese, had had six operations for appendicitis, uterine prolapse, and postoperative hernia, the last one six years ago. For the past four years there had been more or less lower abdominal pain, which she thought due to adhesions. She presented herself for the repair of the postoperative hernia.

Nov. 28, 1917, a large postoperative hernia was repaired. A tumor was found free in the pelvis, 4 by 3 by 3 cm. This proved to be a sac containing degenerated fat—probably an appendix epiploica which had become twisted from its attachment to the large bowel.

*Incarceration of Appendices Epiploicæ in Hernial Sacs*

CASE 51 (172141).—G. G. B., a male, sixty-three years of age, was examined Sept. 12, 1916. Nine months previously the patient had developed soreness in the left lower abdomen, with the formation of a mass which had persisted, and the soreness had been aggravated by exertion. There were no other subjective symptoms. The patient was obese. On physical examination a small mass was palpable above the left internal inguinal ring and there was, separate from this, a left inguinal hernia. Urinalysis, blood, and x-ray examination of the colon were negative.

Sept. 18, 1916, abdominal exploration was done through a low left rectus incision. No disease other than the tumor mass was revealed. This apparently came and went as the sigmoid, which was held tightly against the left internal inguinal ring, became blocked. A large incarcerated mass of omentum which was undergoing necrosis was found in the hernial sac, dissecting its way between the muscles and fascia. Adherent appendices epiploicæ of the sigmoid were also contained in the hernial sac, which held the sigmoid in a fixed position. The omentum was divided and the sigmoid separated from its adhesions. The hernial sac and contents were removed and the internal ring closed with mattress sutures.

CASE 52 (A186645).—A male, aged fifty-one years, was examined Feb. 24, 1917. The patient had been perfectly well until one week previously, when, after lifting a heavy load, he experienced pain in the left groin and a swelling formed which had remained painful and had caused some nausea. Physical examination was practically negative except for a firm, irreducible mass,  $1\frac{1}{2}$  inches by 1 inch, in the region of the left external inguinal ring.

At operation, March 13, 1917, an incarcerated appendix epiploica of the sigmoid was found in a left inguinal hernia. The appendix epiploica was excised and the hernia repaired.

*Appendix Epiploica Producing Intestinal Obstruction*

CASE 53 (A49009).—C. G. G., a male, aged fifty-seven years, was examined Feb. 8, 1911. The patient's health was in fair condition until eight months previous to examination, when he had had a sudden attack of pain in the left lower abdomen, with much distention, followed by soreness for six or seven days. A month later he had a similar spell. Three months later he had a very severe attack with symptoms of in-



testinal obstruction for seven days. He was in bed fourteen days during which time there were much pain, tenderness, and rigidity in the region of the umbilicus, with apparent obstruction in the left lower abdomen. Morphine and chloroform were used to control the pain. The last severe attack was eight weeks before, but the lower abdominal soreness persisted up to the time of examination. There was never any blood in the stool. The patient had lost about 30 pounds in weight, otherwise the general physical examination was negative. A diagnosis of chronic intestinal obstruction with possible carcinoma of the sigmoid was made.

Operation Feb. 13, 1911, revealed obstruction of the sigmoid by a band due to a long appendix epiploica which was adherent across the top of the sigmoid near its middle. Over this a loop of the sigmoid had dropped, causing a rather tight obstruction. The band was divided and appendectomy done for acute appendicitis.

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## CHRONIC ULCERATIVE COLITIS: A REVIEW OF 117 CASES\*

A. H. LOGAN

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Chronic ulcerative colitis was first described as an entity by White in 1888. During the next few years a few cases were found in the London hospitals, and in 1907 the condition was well considered in an English symposium. German authors also have written at length on the disorder, but I have found few articles concerning it published in our country.

Under the heading Chronic Ulcerative Colitis I shall consider those cases for which no definite etiology has yet been found, and leave out of consideration parasitic, tubercular, syphilitic, and mucous colitis. Chronic ulcerative colitis may be defined as a chronic inflammation of the large bowel of unknown etiology, showing all grades of inflammation from a reddened, congested, easily bleeding mucous membrane up to superficial and deep ulceration, with a duration of from many months to several years of either constant dysentery, or a tendency to remissions, as in duodenal ulcer. Different observers have described several bacteria as probable causes; others believe the condition to be the remains of a Shiga or Flexner bacillary infection, while still others believe the amebæ originate the trouble and that they later disappear from the stools. In no instance has any one organism been able, uniformly, to reproduce the disease in animals.

From a study of such cases I am led to believe that there are a number of organisms capable of producing the disease if the body itself is in a receptive condition. The clinical histories many times point to the beginning of the trouble in an epidemic of diarrhea in a neighborhood in which "ptomain poisoning" had occurred following a social gathering, and all of those who were infected and who recovered were well except one. There are also many isolated cases, coming from no known cause.

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but none in which the disease was transmitted from one person to another. In one of our cases, following an ileostomy 8 inches from the ileocecal valve, the bowel discharge was so irritating and acid that large ulcers formed in the surrounding skin, and continued to spread until the discharge was made alkaline by feeding the patient large amounts



Fig. 54 (200522).—Section of colon showing gradations of atrophy and smoothing out of mucosa with constriction at one end. Thickening of bowel wall.



Fig. 55 (200522).—Constricted area of bowel with greatly thickened wall. Polyp (Fig. 54).

of egg-albumen, when the ulcers healed quickly. This opens up a new line of study as to a possible cause in relation to invading bacteria.

The rectum is apparently the point of election for the beginning of the inflammation, and from there it gradually spreads upward. This assumption is based on the evidence that the proctoscope shows definite

lesions low down and normal mucosa above; the x-ray shows more marked involvement in the descending colon and sigmoid, and post-mortem findings show the oldest lesions low down, with more recent ulcers in the upper colon. In three of our cases fresh ulcers were found in the lower ileum. The mucosa first becomes red and congested with



Fig. 56 (217827).—Autopsy specimen showing many ulcers, with smoothing out of mucosa.



Fig. 57 (197656).—Operative specimen showing hemorrhagic areas in mucosa. The small ulcers do not show in photograph.

increased watery secretion, then it bleeds easily and finally breaks down into superficial ulcers. If the condition is severe, deep ulcers, going on to perforation, develop. In one only of our cases did the ulcers seem to be more severe along the colonic bands, as shown by postmortem, and contrary to many published reports. Small round-cell infiltration of the submucosa and muscular layers is very marked. One of the chief

characteristics is the extreme thickening of the wall of the colon and the smoothing out of all the folds of the mucosa, leaving a smooth, glazed surface. This thickening is caused in two ways: Early, by the hyperplasia in the mucosa, and, later, by the fibrosis which develops in the



Fig. 58 (132288).—Normal colon.

deeper layers. After some time the contraction of this fibrous tissue results in a marked narrowing of the lumen of the bowel, which is permanent, and if localized, may result in a partial bowel obstruction.

The disease begins practically always with dysentery, either starting gradually and becoming more severe, little attention often being given

to it at first, or coming suddenly, as a severe diarrhea. It may develop as an isolated case or as one of a number of cases in which the patients are similarly affected by diarrhea, all of the other cases clearing in a short time, and this patient, though treated exactly like the others by the same physician, failing to get well. The diarrhea is at first watery; later the stool usually contains some fresh blood and pus. The number of stools



Fig. 59 (197656).—Loss of haustration up to splenic flexure, above that wider and not so deep. Descending colon a straight, narrow tube.

varies from two or three up to fifteen daily, which may keep up for several years, or the ulcers may become latent, similar to duodenal ulcers, and, during this latent period, the bowels may become regular or constipated. As the rectum is most severely involved, tenesmus is often present—about one-third of our cases showed this condition. Pain is not a severe symptom; in fact, it is more often absent than present, and when pres-



Fig. 60 and 61 (219090).—Similar to Fig. 59 but showing more involvement upward.





ent, it is seldom acute, unless due to a perforation; there is more of a burning, uncomfortable feeling along the line of the colon. Abdominal gas and the expelling of excessive amounts of it caused complaint in many cases. As the ulceration is chiefly in the colon, digestion and food absorption are little interfered with until late in the disease, or if the type of disease is severe; consequently weight loss usually does not occur



Fig. 62 (205023).—Involvement of entire colon.

early. Loss of appetite as a result of the absorption of toxic products is also a factor in the loss of weight. Fever is practically absent until late in the disease, unless subacute peritonitis or perforation occurs. Blood in the stool will depend on the character of mucosal involvement. In some granular conditions without ulceration bleed freely, while some ulcers show no macroscopic blood.

Many patients are able to keep at work for years without much loss of strength or inconvenience, except for the frequent bowel passages, but the majority, after a greater or less time, if the diarrhea is constant, lose strength and are unable to keep up their work; the hemoglobin and weight loss may not be excessive. This is no doubt owing to the fatty degeneration of the body organs, the



Fig. 63 (169514).—Involvement of entire colon.

liver especially, which takes place after the disease has existed for some time. In the remittent type normal strength may return during the periods of remission in the early years of trouble, but as time goes on the weakness becomes more apparent. The disease is essentially one of many months' and, may be, of many years' duration, but when the breaking comes, it is usually very quickly. Perforation

is not uncommon, and in itself is not always fatal without operation. The perforation which comes slowly is often walled off into a localized peritonitis, with some pain and with slight fever and reaction. The body seems to be self vaccinated against the infection. In two of our necropsies the bowel was found widely perforated, and the bowel contents were in the open peritoneum. There was not much peritonitis and no walling off, the wide extent of the perforation showing that it must have been taking place over a long period. Gastric complaint is rare, though occasionally late in the disease reflex vomiting may take place and be hard to control. The patient is generally in good spirits and inclined to look on the bright side of things until very late in the disease.

The diagnosis is based on—(1) The history of an intractable diarrhea which, in the large majority of cases, contains blood, pus, and mucus; (2) by not finding any parasitic or known bacterial cause in the stool; (3) by the proctoscope showing involvement in the rectum and lower sigmoid; or (4) by the x-ray showing the characteristic changes in the colon.

In the present series of 117 cases (74 males and 43 females) it was found that the beginning of the disease is chiefly in the early and strong periods of life, most of the cases starting between the ages of ten and thirty years. This is, of course, the age in which most dietary indiscretions are indulged, and when most opportunity would be given, through such indiscretions, for a new organism to find lodgment in the bowel, or for the ever-present ordinary bacteria to take on pathogenic significance.

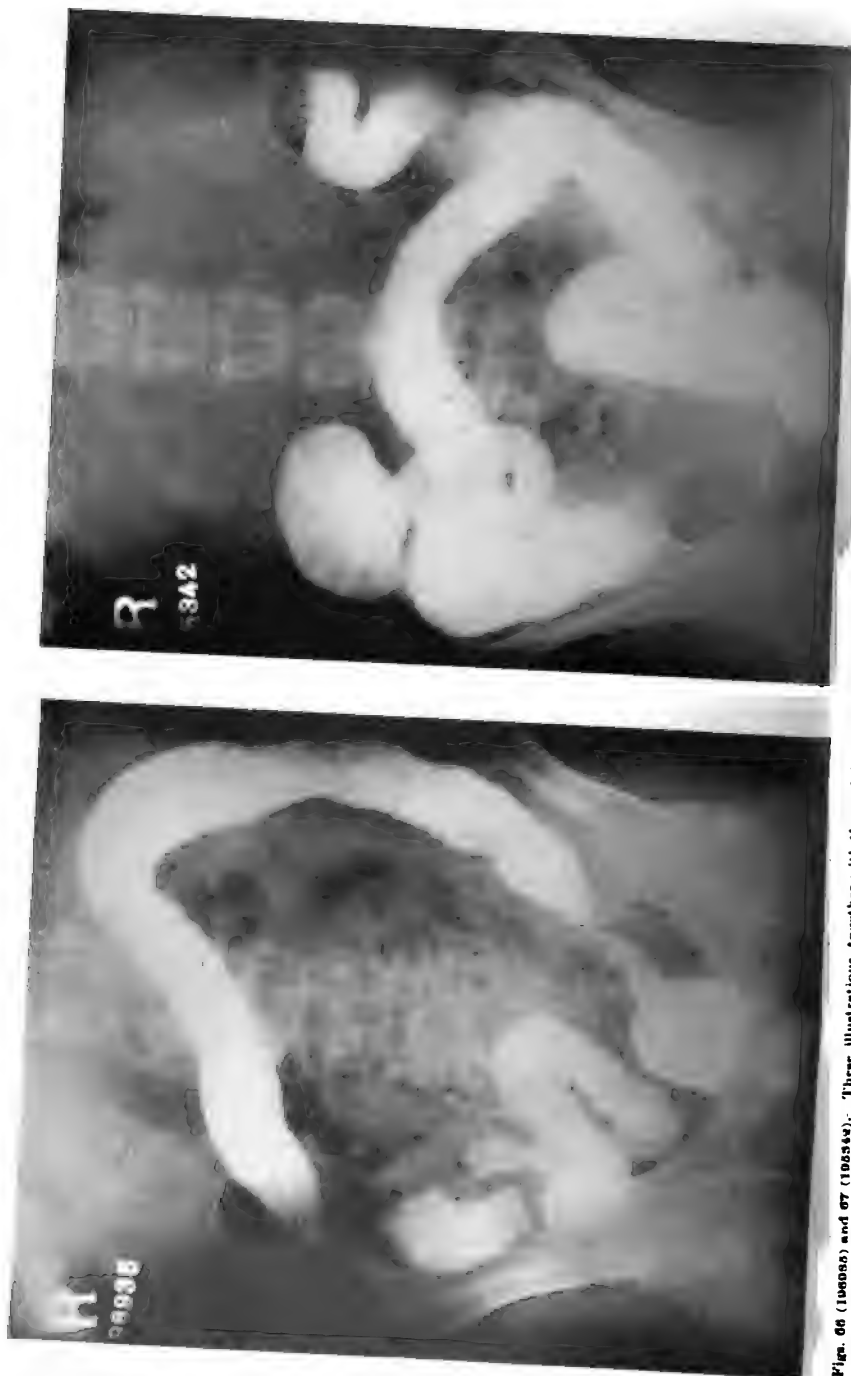
TABLE 1.—AGE INCIDENCE OF THE DISEASE

26	patients were from	10-20	years of age			
39	"	"	"	21-30	"	"
30	"	"	"	31-40	"	"
14	"	"	"	41-50	"	"
6	"	"	"	51-60	"	"
2	"	"	"	61-70	"	"

From the fact that the early stages of the disease are so often free from general symptoms, the simple home remedies are used for a long time before medical attention is sought. When the usual medicines cease to check the trouble, it is let alone to continue as an inconvenience to the patient. Later, when general symptoms begin to show themselves, medical aid is again sought. Our patients have, therefore, come to us some time after the onset of trouble.



Figs. 65 (161207) and 66 (229059).—These illustrations, together with those of Figs. 67, 68 and, 69, show involvement of entire colon, with various stages of contractions and constrictions.



Figs. 66 (105342) and 67 (105342). These illustrations, together with those of Figs. 65, 66, 67, and 68, show development of optic chiasm, with various stages of development and optic chiasm.



Figs. 64 (184551) and 67 (201050).—These illustrations, together with those of Figs. 65, 66 and 67, show involvement of entire colon, with various stages of contractions and constrictions.

TABLE 2.—AGE OF THE PATIENTS WHEN THEY CAME TO THE CLINIC

8 patients were from 10-20 years of age					
40	"	"	"	21-30	" " "
35	"	"	"	31-40	" " "
22	"	"	"	41-50	" " "
8	"	"	"	51-60	" " "
4	"	"	"	61-70	" " "

TABLE 3.—DURATION OF SYMPTOMS

Less than 1 year	18
1 year	12
2 years	15
3 "	12
4 "	13
5 "	8
6 "	8
7 "	2
8 "	2
9 "	3
11-15 years	16
16-20 "	5
20-25 "	1
More than 25 years	2

Symptoms were constant from the start in 51 cases. Many of the patients coming to us were in fair condition, but they were beginning to feel they had less endurance than formerly and that their strength was failing gradually; they realized that the long-time dysentery was sapping their vitality. In many other instances the disease had advanced so far that definite fatty changes had occurred in the liver and heart, and the weakness of the patients was such as completely to disable them or to confine them to bed. In these cases much loss of weight followed. If the dysentery was such as to cause a great loss of blood, anemia resulted, and, as is the case when the anemia is the result of a long-continued seepage, it is harder and takes more time to restore the blood to normal conditions.

TABLE 4.—LOSS OF WEIGHT

14	patients	lost	less than	10	pounds
16	"	"	from	10-20	"
20	"	"	"	20-30	"
19	"	"	more than	30	"

TABLE 5.—BLOOD COUNT

1	patient	hemoglobin	below	20
3	patients	"	between	21-30
6	"	"	"	31-40
12	"	"	"	41-50
9	"	"	"	51-60
18	"	"	"	61-70
27	"	"	"	71-80
15	"	"	"	81-90

One patient only had a red blood count below 2,500,000

During our examinations, seeking a cause for this trouble, an average of three stool examinations on successive days were made for parasites and ova, and the cases in which amebæ or other parasites could be considered the causes were excluded. *Amœba histolytica* was found twice, *Amœba coli* six times, and a non-motile ameba once, but these were considered incidental, as the other findings were typical of the disease. Shiga and Flexner bacilli were not looked for, as it is known that shortly after an acute dysentery from this cause the organisms disappear from the stool, where before they were found in almost pure culture. Complement-fixation tests for Shiga and Flexner bacilli were made, however, in six cases, with practically negative results. Wassermann tests were made in 47 cases, with negative findings except in one case. Gastric contents were examined in 17 cases, in 4 of which free hydrochloric acid was absent; in 2 there was hyperacidity, and in 11 normal acids.

Proctoscopic examination furnished the most information in the early cases, but it is necessarily limited to a small area of the lower bowel. However, it is an invaluable aid to diagnosis, and in early cases the upward extent of the trouble may be thus outlined.

TABLE 6.—PROCTOSCOPIC EXAMINATION

Normal.....	11
Easily bleeding ulcers.....	2
Superficial ulcers.....	14
Severe ulcers.....	47
Granular.....	29
Polyps.....	19

Until June, 1914, we did not use the x-ray in the diagnosis of these cases, but since beginning its use more of the extent of involvement has been shown. Considering the relationship of the pathology in the colon to the x-ray findings, we would expect, in the early stages of any dysentery, to find an irritated condition, in which peristaltic action is rapid. Later on hyperplasia of the mucosa develops, and fibrous tissue is formed in the outer layers. This resultant thickening causes interference with normal peristaltic waves. Each wave is lengthened and is not so deep. It has rounded, not sharp, edges, and when the thickening in the wall of the bowel becomes marked, the colon becomes a stiff-walled tube without haustrations. Finally, with the contraction of the fibrous tissue, narrowing occurs, and often stricture of the lumen results. This is shown in the radiogram of a typical, advanced case by a small contracted colon, smooth, without haustration. In an earlier case the condition is present low down in the colon, and just above the rounded,



wide haustration or the sharply defined haustration, close together, showing either slight involvement or the spasticity of irritation. We have observed some cases, however, in which an advanced condition was shown in the descending colon and an apparently normal condition in the upper colon, yet at operation some involvement was found up as far as the cecum. In cases in which the rectum and rectosigmoid alone are involved it is impossible to make a diagnosis by the x-ray. Occasionally the x-ray shows the trouble in the upper colon with normal bowel below.

TABLE 7.—X-RAY FINDINGS

17 of 80 cases were negative
5 showed spasticity
56 showed chronic ulcerative colitis
43 involved the entire colon
11 involved the descending colon
1 involved the rectosigmoid
1 involved the ascending colon
2 patients were unable to retain the barium

The prognosis in chronic ulcerative colitis is serious. There are a few cures, but mortality is high—7.5 per cent in those patients who stayed in the clinic under medical treatment but a short time, and 27.5 per cent in those patients who underwent operation. It is true that many of the patients had had the trouble a long time and were in the last stage of the disease with the coincident changes, and little or no resistance. It may be that surgical procedures might accomplish more, especially if carried out in the earlier stages of the disease. However, the surgical procedure is in reality only a means of giving some rest to the bowel and of allowing further medical treatment to be given, except in those cases in which partial or complete colectomy has been done. Before coming to us patients had received many forms of treatment without avail, and 38 of them had had some form of operation. The operations were as follows:

TABLE 8.—OPERATIONS ELSEWHERE

Appendix removed	5
Appendix and gallbladder removed	1
Appendix and both ovaries removed	1
Gallbladder drained	2
Some form of rectal operation	17
Appendicostomy	6
Ileostomy	1
Appendix and one ovary removed	1
Abdominal exploration	1
Some pelvic operation	1
Thyroidectomy	1
Rectal polyp removed	1

Not knowing any specific cause for these internal ulcers, insofar as possible, the same principles of treatment were applied that would be applied to an ulcer on the external surface of the body. Soothing and "healing" drugs were alternated with those which stimulate chronic, indolent ulcers. Olive oil was early found to be a good tissue-builder and soother, and is the one agent that stands out as having given the best results. It is taken by mouth, 3 to 6 ounces daily, with from 60 to 90 grains of bismuth. An enema of 3 ounces of olive oil and 60 grains of bismuth is given every night with the patient in knee-chest position, in order that it may be retained as long as possible. Various other sedatives and antiseptics have been tried, but they are not so good as the olive oil and bismuth. Kaolin was of no benefit whatever, although it is advised strongly by German writers. Of the drugs which stimulate, silver nitrate enemas are now used, starting at 1:10,000 and increasing as needed, giving these after a cleansing enema of pure water. I believe that argyrol gives better results than silver nitrate, but on account of its rising price its use has been discontinued. The enemas are given in the knee-chest position, every second or third day, care being used not to distend the bowel.

The greatest benefit in the treatment of these cases has come from the use of heat. With the idea of producing a kind of Bier's congestion, enemas of hot water (120° F. when it enters the rectum) were given, and in two cases in which the involvement was in the rectum and in the rectosigmoid only, healing resulted, with the disappearance of all symptoms after four months of steady treatment. The enemas are given twice daily for from twenty to thirty minutes. Care must also be taken not to distend the bowel, a double rectal tube being used. For those cases in which the entire colon is involved enema treatment is of use only in checking tenesmus and rectal irritation, and for the healing in the lower bowel. While we were unable to find the ameba many times in the stool tests, or to believe that it is primarily the cause of the trouble, the patient has been given the benefit of the doubt and our routine treatment for amebæ, namely, emetin hypodermically, and coal-oil enemas have been used. Slight improvement in one or two cases only has resulted. One cure was reported in the clinic, and one by ipecac irrigations was reported elsewhere. Autogenous colon vaccine has not had a thorough try-out, but thus far it has not given us any definite results.

Rest of the ulcerated area is insisted on in the treatment of external

ulcers, but it is impossible to give absolute rest to the bowel. In order that food residues may be as small and non-irritating as possible, those foods which have any rough wastage, together with those which are highly seasoned and acid, are prohibited; this still leaves a large assortment to keep up the appetite and nutrition to its highest level. To reduce the irritation still more, complete rest in bed was at first insisted on, which did help the dysentery, but usually so weakened the patients that the dysentery eventually took a new start, and the patients were worse off than at first. We now advise as little exercise as possible, but that the patient shall be up and around a part of every day.

Surgery was undertaken first with the idea of introducing medicine through the upper end of the colon and irrigating through, and at first appendicostomies were done. Later, with the idea of removing infected and irritating material and preventing it from passing over the ulcer, thus giving rest to the area, cecostomies and ileostomies were done. Afterward the distal ileum was brought into the wound, also as a means of introducing irrigations. Partial or complete colectomy, which removes the permanently damaged bowel, would be the ideal operation were it not for its serious nature. Medical treatment, through the ileostomy, as I have outlined, is very helpful, though I believe the heat irrigations have given results not obtained by any medical irrigations alone. Given slowly, and with a rectal tube in the rectum so as to prevent distention and spasm, they do a great deal of good. If irritating, they may be made of saline solution or of mild boric-acid or soda solutions.

The 117 cases diagnosed up to April 1, 1918, have been divided as follows: Sixty-six patients either remained in the Clinic a short time under treatment, or were advised as to treatment at home under their home physician's care. Fifty-one patients were operated on and sent home for further treatment. The 66 patients receiving medical treatment only are grouped in table 9.

TABLE 9.—PATIENTS WHO RECEIVED MEDICAL TREATMENT

10 patients treated before 1915	0 deaths
9 " " during 1915	1 death
15 " " " 1916	2 deaths
32 " " " 1917 and to April 1, 1918	2 deaths

The 5 patients who died (7.5 per cent mortality) were extremely sick, with one exception, on their arrival at the Clinic, and died on the fourth, eighth, ninth, eleventh, and thirty-first days respectively. Of

e remaining patients, 42 have been heard from; 4 having died from six months to two years after returning home.

TABLE 10.—REPORTS OF RESULTS OF MEDICAL TREATMENT

3 patients reported being worse . . . . .	3.3 years later
5 " " no improvement from . . . . .	2 months to 2.5 years later
3 " " improvement from . . . . .	1-3 months later
3 " " " " . . . . .	3-6 months later
2 " " " " . . . . .	6-12 months later
8 " " " " . . . . .	1-2 years later
6 " " " " . . . . .	3-3.5 years later
7 " " cures " . . . . .	5 months to 3.5 years later
1 patient " cure for . . . . .	4 years followed by recurrence

TABLE 11.—PATIENTS OPERATED ON IN ADDITION TO MEDICAL TREATMENT

9 patients treated before 1915 . . . . .	3 deaths
9 " " during 1915 . . . . .	2 deaths
8 " " 1916 . . . . .	1 death
25 " " 1917 and to April 1, 1918 . . . . .	8 deaths

Of the 14 patients who died at the time of the operation (a mortality of 27.5 per cent), 5 were listed as being in poor condition, 8 in fair condition, and 1 in good condition. The immediate surgical mortality was 11.8 per cent. Reports of the other patients operated on are tabulated in Table 12.

TABLE 12.—REPORTS OF RESULT OF OPERATIVE TREATMENT

5 patients reported improvement . . . . .	3 months after operation
1 patient reported no improvement . . . . .	3 " " "
1 " " in good condition . . . . .	6 " " "
1 " was so markedly improved that closure of original opening by ileocolostomy was done . . . . .	6 " " "
1 patient was so markedly improved that closure of original opening by ileocolostomy was done . . . . .	14 " " "
5 patients were so markedly improved that closures of original openings by ileocolostomy were done . . . . .	1 year " "
3 patients reported much better . . . . .	1 " " "
2 " " no improvement . . . . .	1 " " "
2 " " much " . . . . .	3 years " "
1 patient " no change . . . . .	2 " " "
1 " " improvement . . . . .	2 " " "
1 " " much improvement after second operation of ileocolostomy . . . . .	1 year " "
12 patients made no report.	

Eight patients were improved enough so that the original opening was closed and an ileocolostomy was done from six months to fourteen months after operation. One patient died as a result of the second operation.

TABLE 13.—TYPE OF OPERATION

OPERATIONS	NUMBER	NO REPORT	MOR- TALITY	NOT IM- PROVED	IM- PROVED	MUCH IM- PROVED	ILEO- COLOS- TOMY LATER
Appendicostomy.....	5	..	1	..	1	2	1
Ileocolostomy.....	1	..	1	..	..	..	..
Resection of sigmoid.....	1	..	1	..	..	..	..
Cecostomy.....	2	..	1	1	..	..	..
Cecostomy and appendec- tomy.....	2	..	1	..	..	1	..
Resection of cecum, ascend- ing colon, and one-third transverse colon.....	1	1	..	..	..	..	..
Appendectomy and ileos- tomy.....	2	1	..	..	..	1	..
Modified Brown ileostomy and appendectomy.....	21	6	2	..	1	6	6
Modified Brown ileostomy..	16	5	7	1	..	2	1

Necropsies were done in 8 of the 14 cases

### CONCLUSIONS

1. Chronic ulcerative colitis is a most serious disease from the standpoint of both morbidity and mortality.
2. No specific etiology is known.
3. It is a chronic disease of long duration, the final stage ending quickly from toxemia or perforation.
4. Nature's effort to cure causes excessive fibrosis with resultant deformity in the colon.
5. All forms of treatment are thus far unsatisfactory. The best results come from dieting and giving surgical rest to the colon, except in cases in which the condition is localized to the lower bowel within easy reach of enemas. Hyperemia of the bowel obtained by the use of hot water (120° F.) has given the best results.
6. After the cure of the ulcer is obtained, marked deformity and stricture of the bowel remain permanently.

TABLE 14.—DEATHS

NUMBER	SEX	AGE	TIME UNDER OBSERVATION DAYS	YEAR	CONDITION	HEMO- GLOBIN	DURATION OF ILLNESS	DURATION OF PRESENT ATTACK	OPERATION
134460	F.	32	4	1915	Too sick and delirious to give history on arrival.	..	2 yrs.	8 wks.	
167383	F.	21	11	1916	Came on cot. Given stimulants from start.	..	All life.	4 wks.	
172507	M.	35	8	1916	Very sick on arrival. Confined to bed.	38	3 yrs.	3 wks.	
180355	F.	35	31	1917-18	In fair condition.	85	7 mos.	..	
213043	F.	45	22	1917-18	Poor condition, in bed 3 months before coming for examination.	70	..	..	
AFTER OPERATION									
49279	M.	55	2	Before 1915	Poor condition.	..	6 mos.	..	Ileocolostomy.
67390	F.	22	4	Before 1915	Fair general condition.	89	4 yrs.	2 wks.	Resection of 10 inches of sigmoid.
94719	M.	26	16	Before 1915	Fair condition.	90	10 mos.	..	Appendicostomy.
96200	F.	..	..	Before 1915		..	..	..	Second operation to close Brown ileostomy.
140401	M.	29	2	1915	Poor general condition, 50 pounds weight-loss.	65	3-5 yrs.	3 yrs.	Brown ileostomy.
132290	M.	20	26	1915	Anemic, wasted.	..	2 yrs.	..	Cecostomy.
160059	F.	28	2	1916	Fair condition; appendicostomy ten years ago.	80	10 yrs.	..	Brown ileostomy.
191890	M.	33	10	1917	Poor condition.	72	4 mos.	..	Brown ileostomy.
194370	F.	22	17	1917	Very poor condition; much emaciated.	49	2 yrs.	3 mos.	Cecostomy.
196935	M.	55	4	1917	Fair condition; weight-loss, 25 pounds.	69	5 yrs.	3 mos.	Brown ileostomy (2 stages).
197656	M.	22	22	1917	Fair condition.	73	4 yrs.	..	Brown ileostomy.
206607	F.	38	4	1917	Fair condition.	..	19 yrs.	1 yr.	Modified Brown ileostomy (two cancer areas in colon).
152292	M.	24	18	1918	Good condition.	80	13 1/4 yrs.	..	Modified Brown ileostomy.
217827	M.	40	16	1918	Fair condition.	45	8 yrs.	7 mos.	Modified Brown ileostomy.
219090	F.	39	36	1918	Fair condition.	42	7 mos.	4 mos.	Modified Brown ileostomy.

TABLE 15.—NECROPSY FINDINGS

NUMBER	CONDITION OF BOWEL	LIVER	KIDNEY	LUNGS	HEART	CAUSE OF DEATH
134469	Small polyps of the cecum, ascending and transverse colon. Marked ulceration throughout with hemorrhagic colitis most in sigmoid and rectum	Very marked fatty change, passive congestion and cloudy swelling	Acute parenchymatous degeneration on chronic nephritis		Slight myocarditis	Markedly fatty liver. Nephritis
167383	Slight ulceration of the sigmoid; colon wall much thickened. Multiple papillomas	Marked fatty degeneration	Marked cloudy swelling	Discrete areas. Bronchopneumonia	Negative	Marked anemia
172507	Moderate ulceration of the lower colon. Marked thickening of mucous lining and polyposis which stops sharply at ileocecal valve. Multiple papillomas	Marked fatty changes. Pan hepatitis	Moderate cloudy swelling	Bronchopneumonia	Negative	Toxemia
189355	Many perforating ulcers of transverse and descending colon leaving wide open colon with only localizing peritonitis. Papillomas	Moderate fatty degeneration	Chronic diffuse nephritis	Hypostatic bronchopneumonia	Some fatty degeneration	Multiple colon perforation. Extreme emaciation
212043	Acute ulcerations of ileum and colon more marked in ileum, up 3 feet; not like typhoid	Moderate fatty change; slight cloudy swelling	Moderate cloudy swelling. Occasionally fat droplets		Negative	No adequate cause found
206607	Perforating ulcer. Carcinoma. Multiple papillomas	Slight fatty change. Marked hyperemia	Slight fatty change. Marked hyperemia		Slight fatty change	Peritonitis
152292	Superficial ulcers of the colon and lower one-half of the ileum	Portal cirrhosis. Moderate cloudy swelling. Moderate fatty change	Marked cloudy swelling. Increased interstitial tissue. Hyaline degeneration	Bronchopneumonia	Increased fibrous tissue. Marked fatty change	Peritonitis (localized). Bronchopneumonia. Fatty heart
217227	Ulcerative colitis with secondary submucous fibrous tissue. Hyperplasia. Edema of the colon	Moderate cloudy swelling. Marked hyperemia	Moderate cloudy swelling. Marked hyperemia	Lobar pneumonia	Muscle normal. Slight increase in fibrous tissue	Pneumonia. Emaciation

		Moderate fatty change. Marked cloudy swelling	Chronic interstitial nephritis	Slight bronchopneumonia	Normal	Purulent bronchitis. Slight bronchopneumonia
219090	Most ulcers in cecum, ascending colon and rectum, superficial and deep. Wall thickened. Ulcers over colonic bands					
196935	Many small superficial ulcers of entire colon; older portion in sigmoid and rectum. Thick walls very fibrous. Pedunculated hyperplastic areas	Very marked fatty degeneration	Slight fatty changes. Nephritis and secondary contraction	Hypostatic pneumonia	Negative	Peritonitis
197656	Ulcers in cecum and ascending and transverse colon. None below. Wall of colon gradually thickened from above down, where lining is of smooth, leathery thickness. Lumen of descending and transverse colon 2 cm.	Cloudy swelling and fatty changes	Marked cloudy swelling		Negative	Localized peritonitis. General anemia
140401	Ulcers in lower ileum and colon throughout. Mucosa gone in some areas. Thickened mucosa in what is left and perforation	Cloudy swelling and edematous	Acute nephritis with congestion	Healed tuberculous	Parenchymatous degeneration	Localized peritonitis. Acute nephritis
160059	Thickened colon wall. Papillomas in descending colon					Peritonitis



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# CARCINOMA OF THE SMALL INTESTINE\*

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According to the necropsy reports from a number of clinics in which the examinations have included many thousands of cases, carcinoma of the small intestine comprises about 3 per cent of all the carcinomas of the entire intestinal tract. It is generally noted that carcinoma occurs in the duodenum more often than in the other parts of the small intestine. Our own records, however, made up almost altogether from those of patients coming for treatment, show that carcinoma has occurred 24 times in the small intestine as compared with 1822 times in the large bowel and rectum, and 1689 times in the stomach. This very great difference is certainly striking, and indicates, for some unknown reason, an almost complete minority of carcinoma in this region.

In our series of cases carcinoma occurred 5 times in the duodenum, 11 times in the jejunum, and 6 times in the ileum, and in 2 cases the lesions were multiple and occurred in different parts of the small bowel. In a few instances the neoplasm was close to the juncture of the duodenum and jejunum, and it was difficult to establish its exact point of origin; it may have been primary in the third portion of the duodenum or in the first part of the jejunum. It should also be stated that carcinoma in the small intestine varied from the typical carcinoma found elsewhere in the gastro-intestinal tract in that in a number of cases carcinomas developed on polyps or papillomas. In a few instances only did we observe the true colloid carcinoma, similar to the ordinary intestinal carcinoma, occurring in the part of the intestine between the pylorus and the cecum.

## CARCINOMA OF THE DUODENUM

A review of the reported cases shows primary carcinoma of the duodenum to be more commonly encountered than carcinoma of the jejunum or ileum. In our own series of cases, however, this incidence is not

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borne out, as we have seen but five cases of carcinoma of the duodenum as compared with eleven of the jejunum and six of the ileum. It should be stated, with reference to these cases of carcinoma of the small intestine, that in some instances the growth was quite extensive and it was impossible to be certain of its origin, though in each instance the person making the examination felt sure that the tumor was primarily a tumor of the small intestine. It is not always possible to differentiate a primary carcinoma of the duodenal mucosa and one originating in the bile-ducts, ampulla, or head of the pancreas, especially after the growth has become extensive. These tumors occur strictly in one of three parts of the duodenum—the supra-ampullary, the ampullary, and the infra-ampullary. About 70 per cent of all carcinomas of the duodenum are located at the ampulla, though probably the most interesting cases for consideration are those in which the lesion is in the first part of the duodenum above the ampulla. It is this portion which is so commonly the seat of an ulcer, and it is of considerable interest to compare the tendency of these ulcers to undergo malignant change with the tendency of the gastric ulcer to change in the same way. So far as I know, no one has ever witnessed the change of a benign gastric ulcer to a malignant one, although from the clinical, surgical, and pathologic evidence that we have at hand we are convinced that such a change takes place, at least occasionally. It seems probable that most gastric cancers begin as cancers, but in some instances in which an inoperable carcinoma is encountered in a patient who has had an increasing stomach trouble for twenty years or more it is reasonable to assume that the cancer has not been present all that time. In the consideration of the surgical treatment of gastric ulcers excision should be the accepted treatment, not only for the purpose of obtaining complete relief of symptoms, but also because the ulcers may be malignant at the time, or may later become malignant. We need not have the same fear of malignancy in cases of ulcer of the duodenum. So far as I am able to interpret the case reports, no clearly defined instances of primary carcinomas of the duodenum which might be mistaken for ulcers have been reported, and there is very little definite evidence to show that carcinoma of the duodenum ever arises from an ulcer. I was unable to find, in the records of the clinic, any evidence that a primary carcinoma of the duodenum arose from an ulcer. This point has been considered very carefully and in great detail by others, especially by Jefferson, who collected 30 cases from the literature in which it is possible that this malignant change took place in a duodenal

ulcer. However, Jefferson states that he is not at all certain that such changes did take place. He reports a case in which he performed a necropsy two and one-half years after a gastro-enterostomy for duodenal ulcer, and there was no evidence of the original ulcer, but there was a duodenal carcinoma of the constricting type just where the ulcer was reported to have been. This case seems most important as a support to the contention that duodenal ulcer may be the base of a duodenal cancer. Bland Sutton reports an interesting case in which a duodenal ulcer was the base of a spindle-cell sarcoma; this was the only case of a primary malignancy of the duodenum that he had seen. At the present time the evidence to show that duodenal ulcer ever becomes malignant does not seem sufficient to warrant a consideration of its excision to prevent recurrence. It is possible that such ulcers will be excised oftener in the future, but the question of malignancy need not be taken into account.

In reviewing our records I found five cases which might be considered as primary carcinomas of the duodenum. In one of these cases a gastro-enterostomy was done for an inoperable obstruction; this relieved the patient for a time. At necropsy, several months later, the pathologists reported carcinoma of the duodenum extending up to the pylorus. In the second case there was a carcinoma of the pyloric end of the stomach, and beginning just below the pylorus, independent of the pyloric tumor, was a malignant papilloma of considerable size. In the third case the original tumor was presumably of the first portion of the duodenum, though the ampulla was obliterated, and from the extent of the trouble it was difficult to determine at just what point it originated. The fourth case was quite similar to the third, and showed extensive malignancy. The fifth case was a large carcinoma originating in the first portion of the duodenum. In addition to these cases, there was one other in which operation was done for obstruction in the jejunum, caused by intussusception produced by a malignant polyp. The necropsy, some time later, revealed a papillary carcinoma of the first part of the duodenum, which apparently had not produced symptoms. The histories of these five duodenal cases indicates that the papillary tumor, which so readily becomes malignant, is one of the most common types of primary carcinoma of the first part of the duodenum. It is this type which seems at times to extend across the pylorus from the duodenum to the gastric mucosa.

### CARCINOMA IN THE REGION OF THE AMPULLA

The exact point of origin of a carcinoma in the region of the ampulla is frequently difficult to determine. It may originate in the duodenal mucosa, in the mucosa of the ampulla or ducts, or in the head of the pancreas. Primary carcinoma in this region, if it obstructs the biliary and pancreatic ducts, as it usually does, presents the same clinical picture, no matter where the growth originates, namely, painless jaundice and great emaciation. The jaundice gradually increases, and in a short time becomes very deep. The emaciation depends on the extent of pancreatic interference, which is apt to be complete, and the loss of weight and strength is very marked. Carcinoma in the mucous membrane of the ampulla is the most frequent type, and also probably is the most amenable to treatment. It is very probable that these cases as a group have not received the consideration in the way of treatment that is warranted. It is apparent that, if the liver and pancreas have been completely blocked for any length of time, radical surgery cannot be considered, although I believe that in some instances the cases may be obtained early enough so that a removal of small carcinomas in the region of the ampulla will be possible. Plastic surgery, in this region, has been very satisfactory in the traumatic and stone cases, and undoubtedly is of advantage in malignant lesions that are slow in developing and in forming metastases.

### CARCINOMA IN THE INFRA-AMPULLARY PART OF THE DUODENUM

In the infra-ampullary part of the duodenum carcinoma occasionally occurs as a primary constricting lesion. Such cases are often diagnosed as cases of pyloric obstruction, though the clinical features are different in that the patient with duodenal cancer and obstruction usually vomits a large amount of material which contains bile and pancreatic secretion. The tumors are usually small and produce a marked degree of obstruction. If they are not attached posteriorly to the vena cava and other structures, they may sometimes be removed satisfactorily. This condition of carcinoma of the third part of the duodenum is suggested when marked dilatation of the duodenum is encountered. The x-ray will often locate the obstruction in these cases. In certain instances it might be quite difficult to state whether the tumor is located in the terminal duodenum or at the beginning of the jejunum.

## CARCINOMA OF THE JEJUNUM

Carcinoma occurs in the jejunum either as a degenerated polyp or as a ring carcinoma, quite similar to the ring carcinoma frequently seen in the large intestine. In the degenerated polyp type there is usually no evidence of the condition until the tumor has been forced down into the lumen of the bowel, so as to produce intussusception and obstruction. These tumors rarely become so large as to interfere with the lumen of the intestine. They may, however, be multiple, as they were in several of our cases. Polyps of the small intestine are not altogether uncommon, and it is well to realize that they may undergo malignant changes. In the ring carcinoma type the onset of the obstruction is gradual, and often the lesion is located with difficulty; the x-ray is helpful in these cases. The tumor is small and is not palpable early in the trouble, although peristaltic waves may be in evidence. On exploration the proximal loop of the intestine will be found greatly dilated and the wall hypertrophied from the gradually increased exertion. At first appearance the dilated small intestine resembles the large bowel. Ordinarily, these tumors do not metastasize early; a liver nodule was, however, noted in one of our cases when the intestinal growth was very small. Often the omentum is sealed to the growth. In one instance, because of this omental attachment, I considered a radical excision inadvisable and made an entero-anastomosis, joining the distended and collapsed bowel. The fact that this patient lived comfortably for eighteen months indicates, I believe, that it was a mistake not to have excised the growth with the attached part of the omentum. Mikulicz reported one case of a patient living ten years after an anastomosis without excision, which would suggest the condition to have been a benign lesion or a very slowly developing malignancy. Radical excision is certainly indicated unless the disease is extensive or presents distant metastasis. Regional lymphatic enlargement does not contraindicate radical excision. We have had eleven cases of carcinoma of the jejunum; in most of these a positive diagnosis could not be made before exploration, and in a considerable number the growth was too extensive to permit radical operation.

## CARCINOMA OF THE ILEUM

Carcinoma of the ileum, like carcinoma of the jejunum, occurs as an annular contracting or ring type, also as a sprouting polyp or car-

cinoma, in which case the growth is a broken-down papilloma. Occasionally the massive developing type of carcinoma is encountered in the jejunum and ileum; the growth is so large and involves so much of the intestine that it frequently is mistaken for tuberculosis. The lumen is not greatly interfered with by the growth, so that it may be very large and extensive before it is recognized; only one such case is recorded in our series. Comparatively few carcinomas have occurred at the ileocecal valve. In nearly all our cases the lesion originated several inches from the valve, and was not associated with it in any way. A number of cases have been reported in the literature in which the growth seemed to arise directly in the mucosa, at the juncture of the ileum with the cecum. Other instances have been cited in which a carcinoma, arising from the ileum or the cecum, had extended across the mucosa of the ileocecal valve. We have seen very few carcinomas at the valve as compared with the number arising at the juncture of the cecum with the ascending colon or of the ileum proper. From the mechanical arrangement of this region of the intestine and the likelihood of repeated traumatization it would seem that carcinoma would not be uncommon in this area.

Cases of multiple tumors in the small intestine have often been reported. In several of our cases the growths were multiple. These may occur as papillary tumors or ring-constricting tumors. In one of our cases there was a tumor in the stomach and one in the small intestine, and in at least two cases there was a tumor in the small intestine and one also in the large bowel. Gruner and Fraser have reported two cases of symptomless tumors occurring in the ileum. The growths arose in the submucosa and were histologically similar to tumors of the appendix as observed by MacCarty. While such neoplasms are histologically malignant, so far as we have observed they never develop to the point of producing symptoms and have never been known to metastasize. True carcinoma of the appendix is rare in our experience, though this type of hyperplasia occurs in about one in every 250 appendixes examined.

The clinical features in a true carcinoma of the ileum are similar to those of the jejunum. Usually the diagnosis is intestinal obstruction, the location of which must be determined at the time of the operation. The x-ray will in some instances make the location more definite. When a papillary carcinoma is encountered, it should be remembered that there may be multiple lesions. The same observation holds in carcinoma of the ileum and carcinoma of the jejunum as regards treatment;

that is, excision should be done if there are no distant metastases and if the local attachments are not too extensive. In case of a very marked obstruction with a great deal of intestinal distention and associated fecal vomiting it will be well to do the operation in two stages, first relieving the obstruction by an enterostomy, and then making a resection. I believe this method of procedure should be followed in any case in which the obstruction is marked. The mortality from operating in cases of acute obstruction is so high that any procedure which will reduce it should be employed. In our series there were six cases of carcinoma of the ileum; four were adenocarcinoma, or the ring type of growth, and one was a degenerating polyp with the resulting intussusception. In one case, inoperable because of the extent of the disease, there was a definite carcinoma in the ileum, high up, and one in the cecum also.

In the present review are 24 cases which I have been able to collect from the records of the clinic. The records show also that during the same period there were 1689 cases of carcinoma of the stomach and 1822 cases of carcinoma of the large intestine. As compared with 24 cases of carcinoma of the small intestine, this would seem to be a smaller percentage than has been reported in other statistics. This may be due to the fact that in our cases the records are of patients coming for treatment, while in the reported cases, in most instances, the series are of those coming to necropsy.

#### ABSTRACTS OF REPORTS OF CASES

##### *Five Cases of Carcinoma of the Duodenum. Average Age of Patients, Fifty-three Years*

CASE 1 (24217).—A man, aged fifty-seven, had had at times a constant, dull, aching epigastric pain through to the back. The patient had not vomited, but had eructated sour gas and sour water constantly, and occasionally sour food. His appetite had been good, but he had become progressively weak since the symptoms began. There were no severe cramps or colics and no weight loss. The test-meal findings were: Total acidity, 94; free hydrochloric acid, 0; combined, 94; lactic acid +; blood +; food remnants + + + +. There was a nodular tumor, movable on inspiration in the right epigastrium. The abdominal veins were engorged. The clinical diagnosis was carcinoma of the pylorus.

June 12, 1909, an anterior gastro-enterostomy was done, and a carcinoma of the duodenum, extending up to the pylorus, with obstruction, was found. The patient died September 12, 1909, three months after the operation.



**CASE 2 (61097).**—A man, aged thirty-nine, had had a severe attack of inflammation of the bowels twenty-two years previously. For twenty years the patient had had spells of "nervous indigestion" lasting for a week or more. He had had a sensation of weight below the umbilicus immediately after meals, and occasionally sour stomach and some gas. Bowel movements had always been loose until within the past year when they were very constipated and symptoms had become more distressing. Gas and vomiting of a sour, digested mass occurred, at first every three to four days, and later was forced every night in order to permit sleep. Gas pain came immediately after meals, and other pain came on two hours after meals. The distress was mostly in the lower abdomen, although there was some in the left iliac fossa. There was some distention. There was a loss in weight of 40 pounds in six months. The test-meal findings were: Total acidity, 24; free hydrochloric acid, 0; and combined, 24; lactic acid +; blood +; food remnants +. A mass was palpated in the epigastrium. The clinical diagnosis was pyloric obstruction.

November 22, 1911, a Billroth No. 2 and a posterior gastro-enterotomy were done. The duodenum was removed down nearly to the common duct, and a piece of the pancreas was removed for secondary carcinoma. Extensive carcinoma of the pyloric end of the stomach and primary carcinoma of the duodenum were found. Beginning just below the pylorus, and very adherent to the head of the pancreas, was a malignant papilloma which distended the upper end of the duodenum to the size of an orange. The pathologic findings were: Adenocarcinoma of the stomach and a carcinomatous papilloma springing from the duodenal side of the pyloric ring.

**CASE 3 (163558).**—A man, aged fifty-two, six months previously began to have cramps in the lower bowels which lasted two hours. A few days previous to examination he had had diarrhea, followed by cramps for three or four days, as many as eight stools a day, slimy, with a sour odor. He had pain in the pit of the stomach one hour after meals, of short duration at first, but which later was constant. He had a ravenous appetite, but had lost 20 pounds in weight since the onset of the trouble. The jaundice, which came on a week previous to his examination, was getting worse and he was emaciated. No test-meal was given. The x-ray showed a redundant transverse colon and sigmoid. Physical examination showed a mass to the right of the umbilicus. The clinical diagnosis was made of obstruction of the common duct, carcinoma (?), or pancreatic carcinoma (?).

July 1, 1916, a cholecystogastrostomy and an exploratory cholecystotomy were done, and a hard, firm mass at the head of the pancreas, which produced obstruction of the common duct, was revealed. The common duct was opened and the finger introduced in order to make sure that there were no stones. The tumor was found to be the cause

of the obstruction. July 6, 1916, a transfusion was done for secondary hemorrhage. Death occurred July 8, 1916. Necropsy revealed a carcinoma of the first portion of the duodenum and head of the pancreas, with obliteration of the ampulla of Vater.

**CASE 4 (143715).**—A man, aged fifty-nine, first came for examination October 19, 1915, complaining of the sudden onset of numbness of the fingers and lower extremities; this had been gradually increasing during the previous ten months. For a year he had had spells of distress in the stomach, the spells coming on two hours after meals and at midnight, and lasting from a week to ten days. Bicarbonate of soda and vomiting afforded relief. He vomited sour material at irregular intervals, often at night; at times the entire previous meal was vomited. His appetite was good. The hemoglobin was 40 per cent. The test-meal findings were: Total acidity, 10; free hydrochloric acid, 0; and combined, 10. The x-ray findings of the stomach were indeterminate. Secondary anemia and pyorrhea 2+ were discovered, and treatment was recommended to clean up the mouth from infection. A bland diet was advised. After three and a half months' treatment at the clinic, followed by treatment at home, the patient returned with all the symptoms aggravated. His appetite had been good, as a rule, but he had lost in weight rapidly during the last two months. He had an icterus of seven weeks' standing. The hemoglobin was 22 per cent. A clinical diagnosis was made of hypertrophic cirrhosis of the liver, ethylism, and secondary anemia.

July 7, 1916, transfusion for secondary anemia was done. Death occurred July 11, 1916. Necropsy revealed carcinoma of the first portion of the duodenum, common duct obstruction, general icterus, and a huge right pulmonary embolism.

**CASE 5 (207423).**—A man, aged fifty-eight, came for examination, giving an eight months' history of daily dull, gnawing epigastric pain without radiation, two to four hours after meals. He had sour and bitter eructations, and vomited from three to nine times a day, often large amounts, with blood and "coffee-grounds." The vomiting afforded much relief. The course of the disease was progressive, associated with a marked loss of weight, strength, ambition, endurance, and appetite. He was constipated, but had no severe pain, jaundice, or fever. The test-meal findings were: Total acidity, 30; free hydrochloric acid, 0; combined, 30; there was a trace of blood and food remnants, 2. A tender fullness in the right epigastrium was noted, but no mass was palpated. The x-ray showed a duodenal ulcer. The clinical diagnosis was pyloric obstruction and carcinoma of the stomach (?) and pancreas (?).

September 15, 1917, a posterior gastro-enterostomy was done, and a pyloric lesion was found, apparently on the duodenal side, which caused obstruction 4. A large mass which felt inflammatory was fixed

to the liver and the pancreas. Death occurred September 16, 1917, and necropsy revealed carcinoma of the first portion of the duodenum (embolism?).

#### SUMMARY OF CASES OF CARCINOMA OF THE DUODENUM

In Case 1 of this group the eructation of food for some months suggested ulcer primarily, although there was no other evidence of ulcer. A tumor mass was palpable and was thought to be in the pylorus until the exploratory incision revealed a duodenal carcinoma. The history of the case furnished no indication that an ulcer was present prior to the carcinomatous growth.

In Case 2 the clinical history is not of much importance so far as the duodenal growth is concerned, since the patient also had a carcinoma of the stomach in addition to the papillary carcinoma of the duodenum. However, a history was given of twenty years of stomach trouble, which suggests the existence of a high gastric ulcer prior to the carcinoma.

In Case 3 the lesion occurred in the region of the ampulla and was so extensive that no estimate could be made of its exact origin.

Case 4 was reported as carcinoma of the duodenum; there is nothing in the history to suggest that it had formed on an ulcer.

Case 5 was first diagnosed as duodenal ulcer. The man was fifty-eight years of age and gave a history of having had trouble for eight months. At operation it was impossible to discover where the tumor originated, though it obstructed the duodenum. The tumor in no manner resembled a duodenal ulcer. The necropsy revealed an inoperable carcinoma, apparently primary in the first portion of the duodenum.

#### ELEVEN CASES OF CARCINOMA OF THE JEJUNUM

##### *Average Age of Patients, Forty-six Years*

CASE 6 (710).—A man, aged thirty-nine, for three months previous to coming for examination had been troubled by gas, rumbling, and sour eructations, and cramping pains in the abdomen, starting on the left side, below the umbilicus, and going to the right. The patient had taken liquid diet from the beginning, but for the past month everything that was eaten was vomited as sour, undigested food. The bowels were in fair condition; the weight loss was 50 pounds. No abdominal tenderness was detected on examination. A diagnosis of chronic intestinal obstruction was made.

October 12, 1907, a resection of twelve inches of the small intestine

and a lateral anastomosis were done. A carcinoma of the jejunum, five feet from the origin, with great obstruction, was found. Pathologic examination showed carcinoma of the small intestine. The patient died at his home some time within a year after the operation.

**CASE 7 (20434).**—A man, aged forty, had had attacks of colicky pain in the lower abdomen, induced by sour food, for twenty years previous to coming for examination. Three months previously he had had an attack of dull, aching pain in the pit of the stomach, regularly one-half to an hour after meals, followed by occasional heartburn and vomiting of bitter food, with relief. Recently there had been retention emesis. The appetite was fair; the bowels were very constipated, save for one attack of diarrhea five months previously. During the past three months he had lost 25 pounds. He was emaciated and cachectic. The test-meal findings were: Total acidity, 50; free hydrochloric acid, 24; combined, 26.

February 27, 1908, an exploratory operation was done, which revealed malignant disease of the jejunum two inches below the duodeno-jejunal juncture. There were secondary nodules in the peritoneum and in the intestines, and free fluid in the abdomen. Pathologic examination of a lymph-gland showed carcinoma.

**CASE 8 (25214).**—An unmarried woman, aged forty-nine, had had curvature of the spine since she was eleven years of age. She gave a history of cough and night-sweats for two years. Three months previous to coming for examination she had had gas on her stomach for three days, with difficulty in expelling it, and a sudden onset of pain in the pit of the stomach that worked down around the umbilicus and up to the costal arch; this lasted one hour. Since that time she had had cramps from fifteen to thirty minutes after meals, lasting an hour, after which there was tenderness over the epigastrium. Occasionally the right costal pain penetrated to the back. There was no nausea or vomiting. The appetite was poor. There was a loss in weight of from 10 to 12 pounds. The bowels were constipated; there was black passage, but no blood. A tumor had been noticed two weeks previously. A mass was found in the left side of the abdomen, and diagnosis of a tumor of the splenic flexure was made.

July 8, 1909, an exploratory operation was done, and a carcinoma was found, beginning at the jejunum, with the involvement running through the mesentery of the small intestines and the region of the superior mesenteric artery. There were movable nodules on the peritoneum. Death occurred at the patient's home October 18, 1909.

**CASE 9 (68893).**—A married woman, aged forty-six, three years before coming to the clinic had had an onset of short spasms of severe pain in the epigastrium, extending through to the back. Morphine was given. There was tenderness afterward, but no fever, no bowel

disturbances, and no vomiting until after the use of the morphin. She also had had headache, and more or less dull pain in the right loin. Her appetite was fair. For the past six weeks the epigastric pain had come on for one hour immediately after meals; there was no vomiting. The bowels were constipated. There was anemia and gradual loss of weight of 20 pounds in three years. The test-meal findings were: Total acidity, 48; free hydrochloric acid, 0; combined, 48. Examination showed a slight fullness in the right hypochondrium and an indefinite cystic left

abdominal tumor.

A diagnosis of gallstones and a left abdominal tumor was made.

June 18, 1912.

an entero-anastomosis was made just below the obstruction. Carcinoma of the upper jejunum was found about two feet below the origin: the growth involved the entire circumference and the mesenteric glands, and produced obstruction, which in time produced a tumor the size of a fist along the mesentery and spine. A small nodule removed from the mesentery was shown to be carcinomatous.



Fig. 70 (85886).—Obstruction of the upper small bowel. The markings of the valve conniventes are clearly visible in the gas and fluid-distended bowel.

CASE 10 (85886).—A man, aged forty-three, nine months before coming to the clinic had had a spell of cramping pain from three to four hours after meals, which was relieved only by induced vomiting. The spells occurred at varying intervals until five months previously, when the trouble became practically continuous, the pain coming on one and one-half hours after eating, with no relief except from induced vomiting of bile and a quantity of foul material which had been in the stomach several days. The patient had had daily lavage and had been able to keep down only a few liquids. The bowels were regular if any-

ring passed through the stomach. The test-meal findings were: Total acidity, 50; free hydrochloric acid, 40; combined, 10; Oppler-Boas, 2; food remnants, 2. The x-ray examination showed carcinoma of the stomach (Fig. 70). A clinical diagnosis of pyloric obstruction and dilated stomach was made.

June 17, 1913, an entero-anastomosis was made, and a ring carcinoma high up in the small intestine and nodules in the omentum, operable on account of metastasis in the omentum, was found.

CASE 11 (86605).—A man, aged fifty-seven, had an onset of trouble with an attack of diarrhea nine months previous to examination. He vomited occasionally a sour, green material from two to three hours after meals, and complained of soreness in the area of the right costal margin and in the epigastrium. He had avoided acids and meats, and had lost 25 pounds in weight and much strength. The bowels were constipated, but there was no melena. The test-meal findings were: Total acidity, 48; free hydrochloric acid, 40; combined, 8; food remnants, 2; altered blood, 1; sarcines, 3. Physi-



Fig. 71 (86605).—Obstruction of the upper jejunum showing gas and barium in jejunum at the point of obstruction; six-hour retention in the stomach and duodenum.

cal examination showed cachexia and a movable, tender, right epigastric mass. The x-ray showed pyloric or duodenal obstruction; the stomach and duodenum both contained a six-hour residue. A loop of small bowel was caught up behind the stomach and contained residue. A diagnosis of jejunoduodenal obstruction (ulcer-carcinoma?) was made (Fig. 71).

July 2, 1913, a resection of the upper jejunum and an end-to-end

anastomosis were made. A jejunostomy five inches below the anastomosis was made for feeding purposes. The operative finding was a spool carcinoma, one and one-half inches below the transverse mesentery of the colon and the upper jejunum. An inflammatory gland was removed from the spine. There was a sharp, horny deposit, a spur of the lumbar spine behind the carcinoma. Pathologic examination showed carcinoma of the jejunum (Fig. 72).

CASE 12 (134048).—A man, aged forty-four, came to the clinic complaining of the onset, six months previously, of a feeling of fullness and weight and distress immediately or soon after meals. This passed away of itself, or after induced vomiting of bile without blood or retained food. The patient had lost 40 pounds in weight in three months, but not much since. For the past two months he had been on light

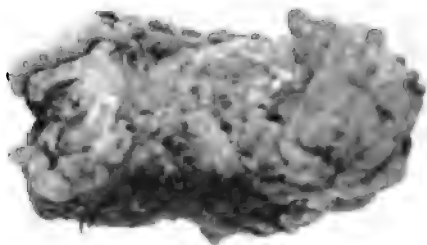


Fig. 72 (86605).—Gross specimen.

diet and had rarely vomited. The bowels were very constipated for the previous month or more. The test-meal findings were: Total acidity, 30; free hydrochloric acid, 22; combined, 14; the food remnants were 17. Examination revealed a mass just below the umbilicus. The x-ray showed a No. 2 residue, a palpable tumor mass, chiefly if not wholly ex-

trinsic, and dilatation of the upper small bowel, evidencing obstruction. A diagnosis of cancer of the colon was made.

June 26, 1915, a resection of one foot of small intestine, including the growth, and an end-to-end anastomosis were made. A primary carcinoma of the small intestine encircling the entire bowel six inches below the duodenum and adherent to the transverse colon was found; the colon was not involved. Pathologic examination showed extensive carcinoma of the jejunum with no glandular involvement.

CASE 13 (151015).—A married woman, aged thirty-four, had had an operation in May, 1915, when eight inches of bowel were removed for inflammation. A button had been used. Two months prior to the operation an abdominal mass had been felt in the right umbilical area. The pain was felt chiefly when the patient was in a reclining position, and she was obliged to lie on her right side. Constipation was marked. A good recovery was made from the operation and she gained eight pounds in weight. Two months later a mass, which gradually became larger, was again felt to the left and at the level of the umbilicus. The patient's

back ached, she was constipated, and injections gave distress. Distention 2. The patient was anemic and thin. The irregular, firm, movable mass suggested carcinoma. A diagnosis of recurring abdominal tumor was made.

Jan. 29, 1916, a resection of eight feet of intestine with a mass of glands, and an end-to-end anastomosis were made. A carcinoma of the upper jejunum about 16 inches from its origin was found. A large mass of glands extended down on to the superior mesenteric vessels, which were probably cut and tied. The transverse colon was dissected free. The growth and the glands were necrotic, very foul, and adherent to the abdominal wall. The blood-vessels ran into the growth and were considerably choked. Collateral circulation could be obtained. Pathologic examination showed carcinoma of the jejunum.

CASE 14 (159902).—A man, aged forty-five, four weeks before coming to the clinic, had an acute attack of abdominal pain, which localized in the right iliac fossa. The patient had kept at his work, and four days previously there had been a very severe exacerbation of pain in the same place, followed by vomiting and, he thinks, fever. A bloody diarrhea and tarry stools and the formation of a mass followed; bowels had not moved for two days prior to examination. The patient could scarcely walk for pain. He had lost 23 pounds in weight. Examination revealed a mass in the right iliac fossa. A diagnosis of appendiceal abscess was made.

May 19, 1916, a resection of 12 inches of the small intestine and an end-to-end anastomosis were done. The operation revealed carcinoma of the small intestine (about the middle of the jejunum), with extensive glandular involvement, which could not be removed. A resection was done on account of the danger of obstruction, from which the patient was evidently suffering. The appendix was not diseased and was not removed.

CASE 15 (189091).—A man, aged sixty-five, had had spells of pain lasting from seven to ten days, with intermissions of from one to three weeks. For three months previously the pain had been almost constant, except during the last ten days. The pain came on for half an hour soon after eating. There was peristaltic unrest and rumbling, and then ease until food or drink were taken. There was no vomiting, no sour eructations, but some gas and belching. The patient's appetite remained good, but he was afraid to eat and had lived on liquids during the past two months. When the stomach was empty he had no pain. He had lost 90 pounds in weight. The bowels were usually normal, but several times during the previous four months the stools had been liquid and there were several movements a day. The food remained just as it had been taken into the stomach. On examination for test-meal findings, the stomach was found to be apparently empty. Pressure on the stomach forced forward a large amount of gas and liquid material;



there was no mass palpable. The x-ray examination showed the stomach and colon to be negative. A diagnosis of chronic intestinal obstruction was made.

April 4, 1917, an entero-anastomosis of a completely distended loop and of a collapsed loop of the small intestine was done. A gland was excised from the mesenteric attachment beneath the growth and a small gland was excised from just beneath the serous coat. An inoperable ring carcinoma of the small bowel, beginning apparently in the jejunum, was found. The bowel up to the growth was markedly dilated, and



Fig. 73 (189091).—Obstruction of the small bowel, showing gas and fluid distention of the bowel.

was almost completely obstructed. Ascites and nodules in the right lobe of the liver, which had the characteristic feel of carcinoma, were noted. Pathologic examination of a specimen from the jejunum showed it to be carcinoma.

CASE 16 (241941).—A man, aged forty-seven, had had two previous operations: One in February, 1917, for the removal of a growth from the left shoulder, and the other in September, 1917, for the removal of glands from the neck and arm (sarcoma?). Two and one-half months

before coming to the clinic the patient had noticed an intermittent pain to the left of the umbilicus and a little below, which came on for a few minutes and then disappeared. The pain was not affected by food as the patient felt well after eating, and there was very little belching and no nausea or vomiting. He was sometimes wakened at night by pain in his side, but had not been kept awake. Two months previous to his examination here he had had an acute attack of pain and a physician was called. There was a weight loss of 20 pounds in four months. The patient was put under observation, and two weeks later, three



Fig. 74 (127339).—Small bowel distention due to low obstruction.

hours after eating, he had an attack of pain, lasting a few seconds, to the left of the umbilicus, and he vomited considerably more than he had eaten for breakfast. This was repeated the following day. The test-meal findings were: Total acidity, 36; free hydrochloric acid, 20; combined, 16. The x-ray examinations of the stomach and colon were negative. The diagnosis was indeterminate.

Sept. 9, 1918, a short-circuiting entero-anastomosis around the tumors was done. The operative findings were: Melanosarcoma (?) or melano-epithelioma (?) of the small intestine, secondary to a melano-

epithelioma, removed from the left shoulder elsewhere. The upper portion of the small intestine was markedly dilated from three tumors involving the mucous membrane of the intestine. The walls of the intestine were adherent to one another, causing obstruction, and were greatly thickened. There were two tumors about three inches apart and 18 inches below the upper tumor, which was situated in the jejunum about two feet from its origin. There were numerous large glands in the mesentery. There were a large tumor in each adrenal region, overhanging the kidneys, and a small tumor in the liver. Pathologic examination of the gland showed it to be a melano-epithelioma.

#### SUMMARY OF CASES OF CARCINOMA OF THE JEJUNUM

Eight of these cases occurred in men and three in women. In most instances the patients had had symptoms only a few months, in some only a few weeks; however, in one case some intestinal symptoms had been present for twenty years, and in two cases symptoms had been present for two and three years respectively. The histories do not show great similarity, and it was almost impossible to diagnose the nature or location of the obstruction, but obstruction was present in every instance. Occasionally the tumors could be felt, although this was not helpful in differentiating. Abdominal pain was severe and colicky, and had occurred intermittently for some weeks. There was no definite localization of the pain, although it was most frequently in one or the other of the iliac fossæ. Weight loss was very rapid, and in most cases was marked at the time of the examination.

#### SIX CASES OF CARCINOMA OF THE ILEUM

##### *Average Age of Patients, Fifty Years*

CASE 17 (907).—A man, aged forty-eight, had begun to lose weight twenty-one months previously. He had had some pain through the abdomen, colicky but never severe. He had been constipated for a year and the abdomen had been distended for six weeks previous to an exploratory laparotomy, in which adhesions were found. He gained weight and had felt well for the next three months, when he again lost weight, and pain and constipation increased. He vomited for two or three days, when there was distention of the lower right side. Examination showed a probable mass in the right hypochondrium, and chronic obstruction (malignant?) was diagnosed clinically.

Jan. 22, 1907, resection of the small intestine and eight inches of ileum was done. Pathologic examination showed adenocarcinoma. The patient died Jan. 30, 1907.

CASE 18 (2263).—A man, aged fifty-three, came for examination complaining of having had constipation and morning diarrhea for many years. He had also had symptoms of obstruction for the previous six months, that is, gas and distention, and at times a great deal of pain across the abdomen, particularly on the left side. Examination showed an irregular mass in the left hypochondrium. A clinical diagnosis of tumor of the splenic flexure was made.

July 10, 1907, a resection of 14 inches of the ileum was done for conglomerative tuberculosis and obstruction. Necropsy revealed carcinoma of the small intestine; the glands of the mesentery were involved.

CASE 19 (9420).—A married woman, aged forty-four, had had attacks of indigestion for ten years, with food distress and gas; vomiting gave relief. For the past year the spells had been worse, with pain in the epigastrium and to the right. Distention, sudden chill, increased pain, black, loose stools, vomiting of a green substance, but no blood, had been noted. Morphin had been given for the pain. The last attack continued for two weeks. The patient had lost 20 pounds in weight. The test-meal findings were: First test: Total acidity, 14; free hydrochloric acid, 0; combined, 14; and a trace of blood; second test: Total acidity, 18; free hydrochloric acid, 0; combined, 18; a trace of blood, lactic acid (?).

June 22, 1908, six inches of the ileum were resected. A fibrous polyp the size of an egg was found; it was causing intussusception of the ileum 18 inches above the ileocecal coil. The pathologic examination showed a malignant polyp of the ileum.

CASE 20 (36824).—A single woman, aged fifty-six, had had occasional shooting pains through the lower abdomen seven months previously. Four months before the onset she had been distressed with gas, three to four hours after meals, and had vomited. Her physician had stated that it was "kidney trouble" and had put her on a milk diet. In four or five days she returned to ordinary diet because of increased distress from gas and nausea, which continued up to the time of our examination, with frequent spells of vomiting. Her appetite had been good. She had lost eight pounds in weight in four weeks; her bowels were constipated, worse during the last four months, but during this time she had had two attacks of diarrhea, lasting from two to four days. The test-meal findings were: Total acidity, 34; free hydrochloric acid, 26; combined, 8. An irregular firm mass filling the pelvis and to the left was palpated. There was a small nodule in the vagina. The clinical diagnosis was pelvic tumor (malignant?).

April 27, 1910, the small intestine was resected; 14 inches of the ileum were removed for carcinoma of the lower ileum; a subtotal abdominal hysterectomy was done; both ovaries and tubes were removed because of secondary carcinoma, and a section of the bladder was also

excised because of secondary carcinoma. The pathologic examination showed carcinoma of the uterus, tubes, ovaries, and of the intestine. May 1, 1910, the patient died of general peritonitis.

CASE 21 (88325).—A man, aged fifty-four, two years previous to coming for examination had begun to feel as if his stomach were filled with gas immediately after eating. He grew gradually worse, but his appetite remained ravenous. As soon as he had eaten the epigastrium became sore and painful. He seldom vomited and never vomited blood; the first time the vomitus consisted of the food eaten the previous day, and after that of the food eaten several hours before. He had from three to four bowel movements a day, but there was no blood or tarry stools. The test-meal findings were: Total acidity, 8; free hydrochloric acid, 0; combined, 8; food remnants, 1. The x-ray showed an hour-glass stomach and obstruction at the pylorus, probably ulcer. Gastric ulcer or probable carcinoma was diagnosed clinically.

July 26, 1913, a lateral entero-anastomosis around the carcinoma was done. The operative findings were: Inoperable carcinoma of the cecum, with secondaries in the omentum, adherent to the posterior outer abdominal wall without obstruction, a carcinoma high up in the ileum, about the middle of the small intestine, with marked obstruction, and a ring carcinoma, probably the primary origin. Death occurred August 5, 1913. Necropsy was refused.

CASE 22 (250604).—A man, aged forty-seven, had had, beginning four or five weeks previous to examination, spells of epigastric fullness with nausea and vomiting of brown, coffee-ground material. There had been a cramp-like midabdominal pain, causing the patient to double up, and an unusual rolling of the bowels. The spells came on after a day of constipation, and were relieved by enemas. The constipation was followed by an unusual thirst and diarrhea for from one to two days. The patient's appetite had been good between attacks; he had lost 34 pounds in weight. The test-meal findings were: Total acidity, 12; free hydrochloric acid, 0; combined, 12. Examination revealed free fluid in the abdomen and increased peristalsis. No masses were palpated. The left epigastrium was enlarged, but not tender. The x-ray examination showed obstruction of the small intestines. A diagnosis of partial intestinal obstruction was made (Fig. 75).

Nov. 13, 1918, a resection of about three inches of bowel with the tumor mass was done, and an end-to-end anastomosis was made by splitting the distal ileum about one inch to increase its circumference (C. H. Mayo method). A small ring carcinoma of the ileum was found completely encircling the bowel 18 inches above the ileocecal valve and forming complete obstruction. The entire small intestine proximal to the growth was enormously distended, very thick walled, injected, and edematous. The carcinoma had perforated through the serosa, but there was no apparent glandular involvement and no metastasis could

made out. There was free fluid in the abdomen. Pathologic examination showed ring carcinoma of the ileum. The patient died November 18, 1918.

#### SUMMARY OF CASES OF CARCINOMA OF THE ILEUM

In four of the six cases of carcinoma of the ileum the symptoms were of short duration, being present from one to twenty-one months. In one case there had been indefinite intestinal symptoms for ten years, and in this particular instance the lesion formed on a degenerating atrophy of the ileum.

The tumor might have been producing the symptoms all these years. In one case there was

history of diarrhea for two years.

The principal lesion was a carcinoma of the cecum, and the tumor in the ileum was not responsible for the symptoms. It was impossible to determine the location of the tumors from the clinical histories,

and in most in-

stances a general diagnosis of intestinal obstruction was made, just as in the cases of tumors of the jejunum.



Fig. 75 (250804).—Gas and fluid distended small bowel due to low obstruction.

#### TWO CASES OF MULTIPLE CARCINOMA OF THE SMALL INTESTINE

**CASE 23 (75198).**—A man, aged sixty-eight, three months before coming for examination had had an onset of doubling epigastric pain with distention and sourness after almost every meal. The patient thought that the gas did not pass up or down. When the pain was severe, it went through to the back. For a month he had been eating nothing but kumiss on account of the pain. There was no jaundice or vomiting. The weight loss was 30 pounds. The test-meal findings

were: Total acidity, 48; free hydrochloric acid, 0; combined. Examination revealed a small mass in the right iliac fossa which was quite movable, also a small mass low in the left epigastrium, and a nodule below the right axilla. Possible carcinoma of the stomach with probable metastasis was diagnosed.

Nov. 12, 1912, an exploratory operation was done. Many large tumors the size of a lemon, encircling the small intestine in different areas, but not narrowing the lumen, were found; there was no obstruction. The glands of the mesentery were involved and there was free fluid in the abdomen. One large mass was found in the pelvis. The condition did not appear characteristically malignant. Pathologic examination of a gland from the mesentery showed carcinoma. Death from pulmonary embolism occurred Nov. 24, 1912.

CASE 24 (145438).—A married woman, aged fifty-six, came to the clinic vomiting. The husband stated that the vomiting had persisted for the previous two and one-half months, and at the onset much bile had been noted. The patient had no appetite and she experienced a great deal of abdominal pain. The bowel movement was somewhat difficult. She was able to drink water and thinks that this had "preserved" her. She had eructations and some gas. Lying on the right side seemed to relieve the vomiting. Examination showed marked emaciation, nausea and retching, and a suggestion of a mass or fullness in the right abdomen. A diagnosis was made of gastric obstruction (carcinoma?).

Nov. 15, 1915, resection was done of three feet of bowel, beginning three and one-third feet below the jejunum. A side-to-side anastomosis was made. The operative findings were a broad-based, pedunculated cauliflower-like carcinoma of the jejunum about four to five feet from the origin, with intussusception of three feet of bowel. The exploration of the stomach and the duodenum was negative. The common duct was greatly distended. The pelvis and appendix were not examined. Pathologic examination showed a broad-based, pedunculated carcinoma with extension through to the serosa. Death occurred Nov. 16, 1915, and necropsy revealed a papillary cystadenoma of the jejunum (removed at operation), a papillary cystadenoma of the duodenum, cirrhosis of the liver, cholangitis, and chronic cholecystitis (strawberry type) with papilloma. There was no metastasis.

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## THE UTILITY OF END-TO-END ANASTOMOSIS BETWEEN SMALL AND LARGE INTESTINE\*

D. C. BALFOUR

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The restoration of the continuity of the small and large intestine following resection of the ileocolic coil is not the least important step in the operation. The exploitation of colonic resection for intestinal stasis has at least resulted in demonstrating the disadvantages of lateral anastomosis between the small and large intestine, and in the rather general adoption of end-to-side union. The latter method has no seriously objectionable features, but it involves two steps which are essentially additional, namely, the closure and inversion of the end of the large bowel and the formation of a separate opening in it for the implantation of the end of the small intestine. Axial union in any part of the intestinal tract is manifestly superior to all other methods, provided the operation can be done with safety, with the preservation of good function, and with the avoidance of late complications.

Recently Lockhart-Mummery has exposed some of the fallacies in the attitude toward axial union of the large intestine, showing that the relatively high mortality and morbidity from leakage are not due to inherent faults in the operation, and has described a method by which end-to-end anastomosis of the colon can be done with safety.

A more or less analogous situation exists in regard to end-to-end anastomosis of small and large intestine. It is quite evident that axial union between ileum and colon is given little or no consideration in the literature and, in so far as we are aware, the procedure is not utilized to any extent among surgeons in this country. Our experience has shown that end-to-end anastomosis of ileum and colon can often be easily and safely performed, which leads us to believe that the general attitude toward the operation is unwarranted. It is for this reason that I bring the method to your attention.

\*Presented before the Southern Surgical Association, St. Augustine, Florida, December 11-13, 1917. Reprinted from *Surg., Gynec. and Obst.*, 1918, xxvii, 249-252.



It should first be said that we have thus far recognized the apparent limitation of axial union to those cases in which there is a dilatation



Fig 76. —Carcinoma of the ascending colon with dilated cecum, dilated ileum, and contracted colon. Omentum dissected back, preliminary to resection.

the small bowel, due to a chronic obstruction from some well defined pathologic condition such as cancer (Fig. 76), or hypertrophic tuberculosis. Under such circumstances, the method has been exceedingly

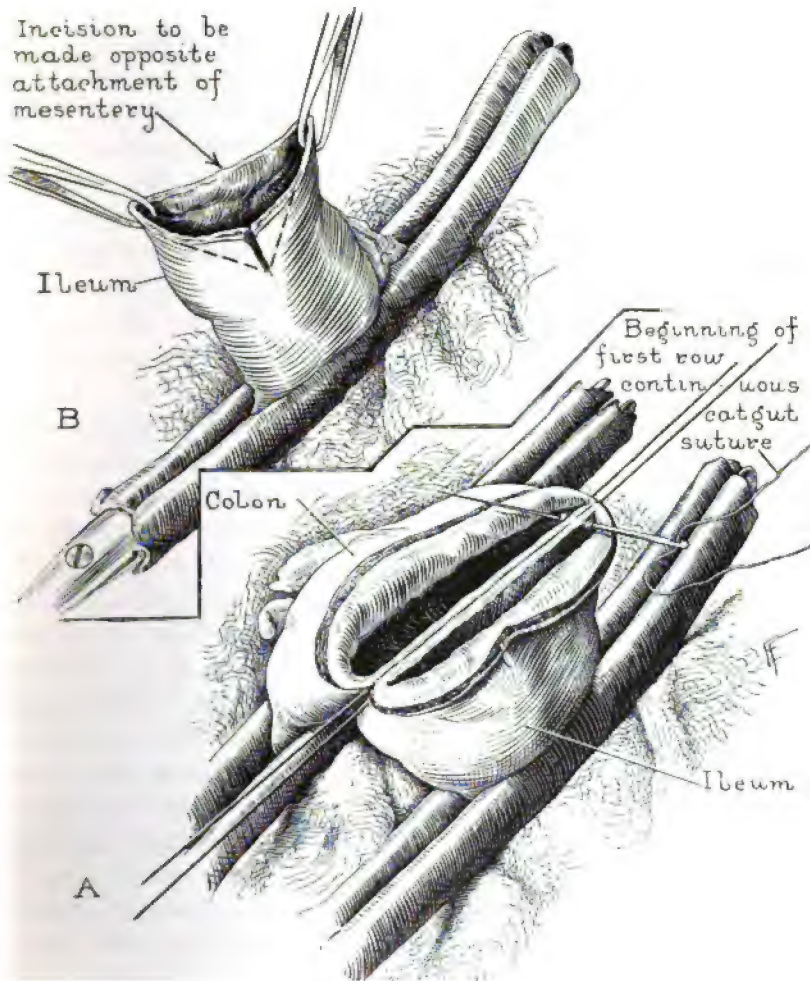


Fig. 77.—A, Ileum and colon aligned and posterior row of sutures begun; B, method of increasing caliber of ileum when not of sufficient size for direct anastomosis.

**satisfactory** Resections of the ileocolic coil for conditions other than those associated with such definite pathologic processes are relatively **rare** in our clinic, but when these other indications do arise, and the ileum is small, there seems to be no reason for abandoning the end-to-side

recommendation. We believe that if the operation is carried out with strict attention to every detail, the utility of axial union of small and large intestine will be quite apparent.

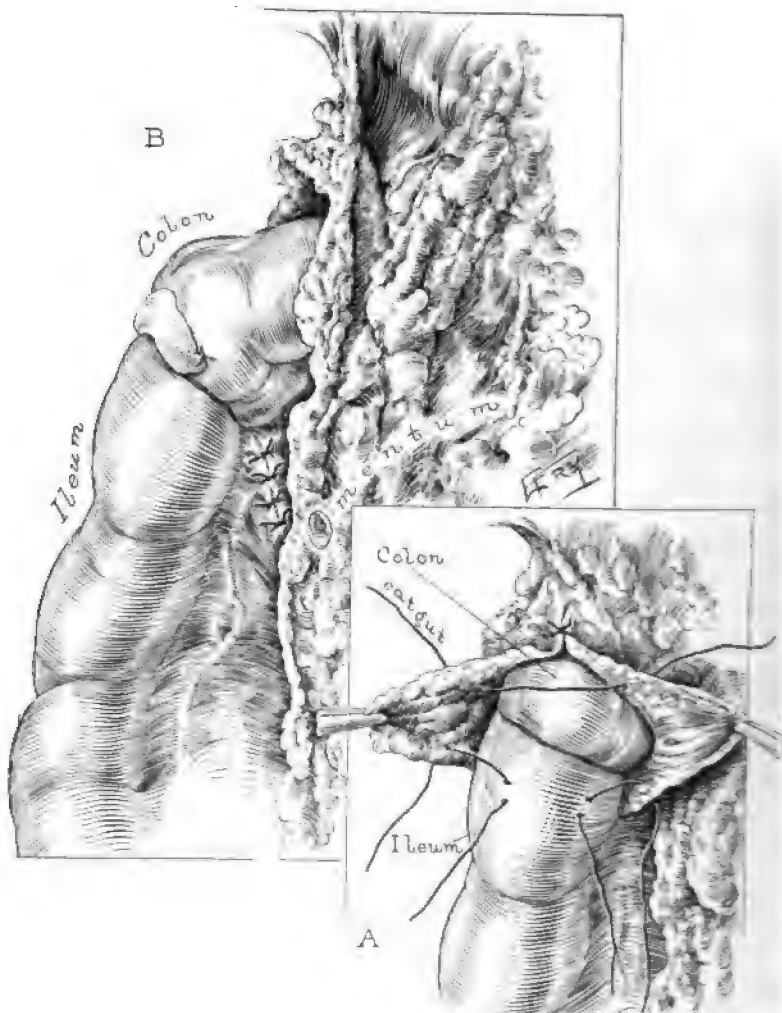


Fig. 80.—A, Anastomosis completed and omental cuff prepared for fixation over suture line; B, anastomosis completed and protected by fat tag, when omentum is not available.

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away with scissors until all coats of the bowel are flush with one another. The union of the segments is then accomplished by a continuous suture of chromic catgut. This suture begins laterally from the mucous side, including all the coats of the intestine, first uniting the posterior walls (the stitching being greatly aided by traction on the sutures originally placed) and continuing anteriorly around the circumference of the bowel, by the C. H. Mayo method, until the starting point is reached (Fig. 78). Two points deserve emphasis in connection with this suture: first, the stitches should be taken close enough to the cut edge of the bowel so that the circulation will not be impaired, and, second, that no catgut should be left exposed. The gloves, instruments, and the anastomosis are now thoroughly cleansed. A reinforcing musculoperitoneal suture of fine silk is placed around the anastomosis (Fig. 79), the two borders of mesentery are brought in apposition by catgut sutures, and finally the anastomosis is protected by available omentum, or fat tags (Fig. 80). This protection may be most satisfactorily made by utilizing a collar of omentum (which can be stripped back before the intestine is resected, Fig. 76), to surround the anastomosis very much as the intestine itself is used to

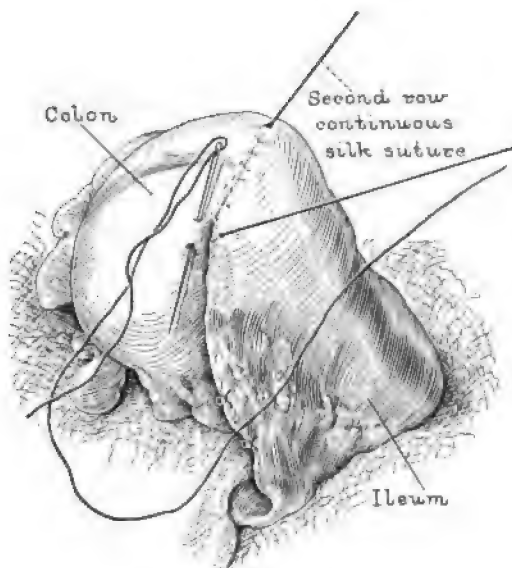


Fig. 79.—Second suture of silk completing anastomosis anteriorly.

protect the suture-line in the tube method of anastomosis. The entire field is now cleansed, gloves and instruments are changed, and the wound closed without drainage. Drainage predisposes to fistula, and should be omitted unless exceptional circumstances demand it.

The results obtained by end-to-end anastomosis between ileum and colon conducted in this manner, have been excellent, and having proved the safety of the method, its obvious simplicity is sufficient for its

cause much pain, and I have seen a few patients who complained of the passing of gas with the urine as the first symptom. The true diverticula are very tortuous and the point of perforation is not larger than a sewing-needle. I have not known these conditions to follow an acquired form of diverticulum. The patient's story is often considered incredulous, and it is believed to be impossible that such a condition should exist without the urine passing back into the rectum. The cystoscopist examiner often fails in his first examination. There being no back flow in the diverticulum, the use of methylene-blue solution in the bladder and the testing of the rectal contents is of no aid.

Through an abdominal incision it is easy to separate the fistula from the bladder and successfully to close it on the bladder side, but on the bowel side it must be dissected out of the wall of the intestine or there is danger of recurrence of trouble, not necessarily a fistula. In some cases the local disease of the sigmoid is so extensive that a resection of several inches of bowel is necessary. This is safely done as the three-stage Mikulicz operation, which, unfortunately, requires a considerably longer hospital attention than does the resection by suture, or the tube resection, in which the union is made over a large tube passed through the rectum and out of the anus. In cases of perforating diverticulitis, obstruction, a common symptom of the usual form of the disease, is not present. Years ago, when the majority of operations for appendicitis were done in the acute stage, cecal fistulas were common. None of the fistulas or colostomies are more difficult to care for than the wet cecal fistula. The change of bacterial flora from ileum to colon makes a great difference in the intestinal discharges. The practically odorless contents of the lower ileum is noted following the Brown ileostomy within six inches of the cecum and is in marked contrast to the contents noted in the cecostomy. After the occurrence of a cecal fistula, the surgeon who does the primary operation for its closure should accomplish it through an ample abdominal incision on the inside of the fistulous opening.

#### OPERATION

Adhesions are separated, complications dealt with and the opening closed, but if the operation is the fourth or the sixth, and there is no obstructive symptom associated with the nuisance of the fistula, the simplest procedure, in order to avoid again dealing with the adhesions and poor intestinal areas for suturing, is to divide the ileum moderately close to the ileocecal valve, invaginating the lower end and making an

side-to-side anastomosis of the proximal end with the sigmoid (Fig. 81). In some instances this can be done with the transverse colon instead of the sigmoid. This immediately dries the fistula, and only occasionally it is necessary to add a few stitches after separating the mucous membrane from the skin to secure closure of the fistula. The operation is



Fig. 81.—Short circuiting for recurring right colonic fistula.

quickly done and is exceedingly satisfactory. Very rarely after these operations is there reverse peristalsis, causing an accumulation of fecal material in the cecum and ascending colon. In such cases Ochsner's permanent mucous drainage is most effective. The colon is divided several inches proximal to the anastomosis, the lower end is closed and the upper end brought into the incision, reducing the size of its lumen

around a small tube and leaving the mucous surface without invagination. The stump of the distal ileum is also brought into the wound so that the functionless large bowel may be emptied of its contents by invagination through this; one fistula only remains and discharges but a little mucus each day. In a few instances in which I have been compelled, as a first consideration, to conserve the strength of the patient, I have found the method most satisfactory. There is no question but that many fistulas heal without operation, the types being those in which the fistulous opening comes close to the parietal peritoneum without an intervening cavity, and this is true whether the fistula is in the vagina or through the abdominal wall. Injections of various pastes into the latter to aid in the healing is an unnecessary procedure, and in those with internal pockets such treatment is usually a waste of time except as a means of diagnosis with the x-ray, as they indicate whether or not a pocket is present.

Practical observations and many years of surgery show that most methods of closure or suture of the small intestine will hold, as it is easier to suture water-tight than gas-tight. A different bacterial flora is found here from that in the large intestine, and the patient, if need be, will die of obstruction or toxemia before the suturing will give way, but the large bowel must be both gas- and water-tight. The most essential point in these operations for fistula of the sigmoid is to provide for a gas vent, which is obtained by placing a tube with a quarter of an inch lumen in the rectum; the tube may be larger or smaller, according to the case. The abdomen being open, the tube is passed into the bowel through the fistula from above before closing. The side of the tube is sutured to the fistula, allowing its end to extend two inches higher within the intestine; one or two extra openings are made in the tube. Slight traction on the tube from the anal exit helps in the application of purse-string or other forms of sutures to close the fistula. Larger tubes become quite painful as they pass through the anal ring. To relieve this condition and to insure an absence of gas tension, the sphincter ani may be split anteriorly with an electric or Paquelin cautery at the close of the operation. In the case of a vaginal fecal fistula, splitting the sphincter ani in this manner renders a tube unnecessary. This being done with the cautery, there is no infection, and granulation tissues soon protect the area. Vaseline is freely applied, and the contraction of the burn usually closes the muscles to perfect function. When the intestinal wall is much infiltrated around the area of the fistula, an appendicostomy.

h a catheter inserted, has often been of great aid in delivering gases in the proximal side. After the second day, a small injection of water through this tube a couple of times a day is of advantage. Should a tight gas fistula be noted on the fifth day, the tube has probably been allowed to accumulate fecal matter. In cases of primary and unexpected fistulas which are passing gases and liquid feces, if the nurse will see that the rectum is kept emptied a considerable percentage of such fistulas will close without other operation. The dry, hard material accumulates and cakes in the rectum and will not be found without digital examination.



## PRIMARY RETROGRADE INTUSSUSCEPTION OF THE SIGMOID ASSOCIATED WITH TUMOR\*

D. C. BALFOUR

We have recently observed, in the clinic, a most striking example of a retrograde intussusception occurring in association with a sigmoidal tumor.

Power, who made such valuable contributions to the subject of intussusception, states that about 5 per cent are of the retrograde type. However, it is quite obvious from such records as are available of these reverse types of intussusception that the case I present is unique for the reasons that the condition was primary and had not developed as a complication to an intussusception of the usual variety, that it was not a terminal event in peritonitis or obstructive vomiting, and, finally, that the method of its production could be observed at operation.

The patient (Case A203308), a male, aged forty-five years, presented himself for examination Nov. 17, 1917. He had been in good health (the appendix had been removed twelve years previously) until Oct. 1, 1917, when a diarrhea began, with from eight to ten watery stools a day, but without blood or mucus. The general physical examination was negative except for a slight abdominal tympany. The blood, stomach contents, urine, and the Wassermann test were negative, as were also repeated proctoscopic and stool examinations. The customary therapeutic measures were suggested, but on March 4, 1918, the patient returned to the Clinic reporting that the diarrhea, still without blood or mucus, had persisted. He had been disturbed by considerable flatulence and borborygmus, and by occasional moderately severe abdominal cramps—the history of an intermittent obstruction. The general examination again was negative, but x-ray of the colon showed a filling defect high in the sigmoid, a finding which remained after antispasmodics had been administered. March 30, 1918, the patient was sent to the hospital, and an exploration (W. J. Mayo) through a left rectus incision revealed a mass in the pelvic sigmoid. There was

\* Dr. V. C. Hunt has kindly assisted me in reviewing the literature of the subject. Submitted for publication Nov. 16, 1918. Reprinted from *Ann. Surg.*, 1918, lxxviii, 588-590.

arked obstruction from the tumor, the sigmoid above the growth showing great distention and muscular hypertrophy. On further examination of the tumor (which through the bowel felt like a bunch of angle-brims) it was discovered that a retrograde intussusception had occurred (Fig. 82), and that the tumor and the section of bowel involved had been intussuscepted upward about three inches. Within a minute or two after the reduction of the intussusception (Fig. 83), which could readily be done by traction, a strong reverse peristalsis was manifest, and the tumor was again drawn upward by powerful antiperistaltic contractions of the proximal sigmoid, these contractions extending upward for a distance of from 12 to 14 inches above the site of the tumor. The process of invagination, begun in this manner, continued until the portion of



Fig. 82.—Appearance of retrograde intussusception at operation.

the bowel containing the tumor was drawn upward and completely engulfed by the proximal segment (Fig. 84). Ten inches of the sigmoid, including the growth, were resected. An end-to-end colonic anastomosis was done, and the suture line was drawn through the omentum (C. H. Mayo method). There were no enlarged glands, and exploration of the liver and peritoneal cavity was otherwise negative. The tumor itself proved to be a pedunculated malignant papilloma 10 by 15 cm. The abdomen was closed without drainage, but two small rubber tissue drains were inserted down to the peritoneum and a tube was stitched in the rectum. The convalescence was uneventful.

The various theories as to the factors necessary to produce an ordinary intussusception may be applied in explaining retrograde intussus-

ception in the colon. The first and most important fact is that, normally, muscular contractions in the large bowel are, at times, antiperistaltic.

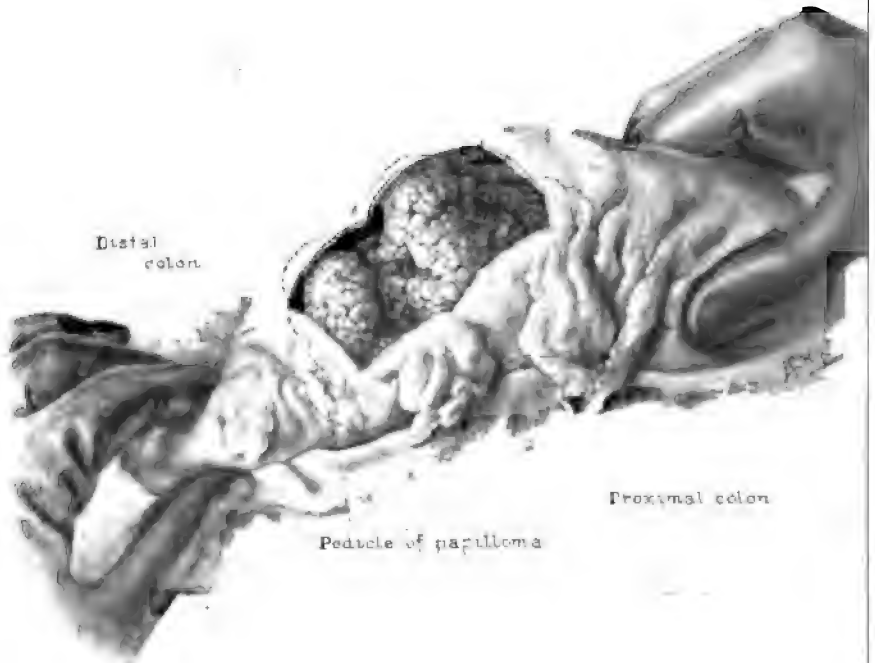


Fig. 83.—Intussusception reduced, portion of wall of sigmoid removed to show the tumor in situ.

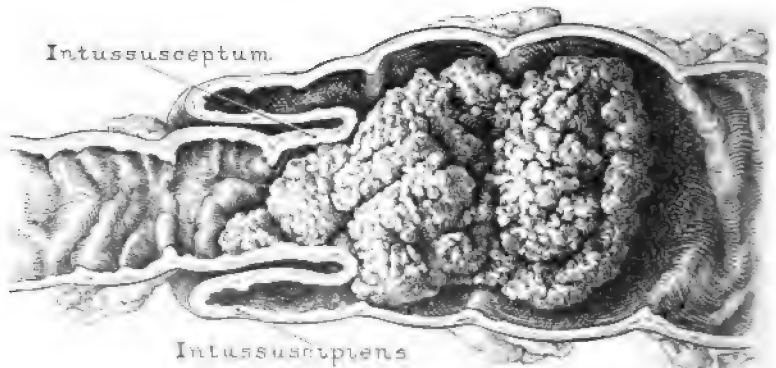


Fig. 84.—Diagrammatic representation of intussusception and tumor cut longitudinally.

This is not true of the small intestine, consequently retrograde intussusception in the small bowel is almost always a terminal event, associated either with an ordinary intussusception or with the reverse peri-

alsis of obstruction. In the large bowel antiperistaltic waves have been demonstrated by Cannon, and he has shown that these waves may be produced by a tonus ring, although the conditions which establish the rings are not as yet determined. These antiperistaltic waves, which are the primary causative factor in retrograde intussusception in the colon, were, in our case, undoubtedly initiated by the tumor, the attachment of the base of the tumor causing a tonus ring just as such rings may be caused experimentally. Further, pedunculated tumors are the only variety in which an intussusception may occur; carcinomas, diverticulitis, and inflammatory tumors involve the intestinal wall to an extent sufficient to produce a rigidity which prevents invagination, and these tumors are not pedunculated.

The rarity, therefore, with which tumor formation in the sigmoid is associated with intussusception is because of the rarity of the type of tumor essential to such an occurrence. Given the factor of irritation, abnormally strong peristaltic waves are produced both above and below the site of the tumor. In the case under discussion not only did the tumor act as a point of irritation, but also the polypoid mass, which was the size of a large orange, lay free in the colon, and as the powerful contractions of the hypertrophied musculature of the colon gripped the tumor, they exerted enough pull on the base of the tumor to begin an invagination and a true retrograde intussusception. This invagination was aided, of course, by other factors, the most important of which were the difference in caliber of the bowel above and below the point of partial obstruction occasioned by the growth, the spastic condition in the lower segment, and, finally, a sufficiently long mesentery to give free mobility.

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## PRACTICAL CONSIDERATIONS WITH REGARD TO PERMANENT COLOSTOMIES\*

W. E. SISTRUNK

Each year we see a number of patients in whom we find it necessary to make permanent colostomies. As a rule, these colostomies are made in certain patients selected from a group of cases in which it has been found necessary to excise the rectum and sphincter muscles for cancer, and in cases of inoperable cancer of the rectum. The patients thus operated on have given us excellent opportunities to test the various types of operations and to note the annoying conditions which may arise following a permanent colostomy.

In reviewing briefly the anatomy of the lower colon, it will be remembered that the posterior one-third of the descending colon, from the splenic flexure to the sigmoid, usually lies behind the peritoneum. This portion of the bowel has, as a rule, a very short mesentery, and often is more or less fixed to the posterior abdominal wall. Near the beginning of the sigmoid flexure the peritoneum completely surrounds the bowel, and the mesentery supplying this portion becomes much longer; it usually measures from three to six inches in length.

Nearly every type of colostomy that has been suggested and that seemed practical has been used in the Mayo Clinic, but up to the present time operations, or procedures undertaken with an idea of giving the patient control of the bowel passages have almost always proved disappointing. Until recently we made the majority of colostomies through an oblique, muscle-splitting incision in the left inguinal region. The loop of bowel brought up for the colostomy was supported by a glass rod, a rubber tube, a piece of skin or silk-worm sutures, and was cut across five or six days following the operation. Many of the colostomies made in this manner were perfectly satisfactory. In a few of the cases there was a tendency toward the development of a ventral hernia into the tissues surrounding the colostomy. More frequently, however, the

\* Presented before the Southern Surgical Association, Baltimore, December, 1918. Reprinted from Surg., Gynec. and Obst., 1919, xxviii.

tendency has been toward a retraction of the loop of bowel in which the colostomy was made, allowing, in some instances, the proximal end of the bowel to discharge a part of its contents into the distal end. We also have found, in instances in which the bowel was cut off at or near the level of the skin, that there is a tendency on the part of the skin to contract around the opening in the bowel, thus narrowing it sufficiently to interfere with the proper discharge of feces. In looking back on the

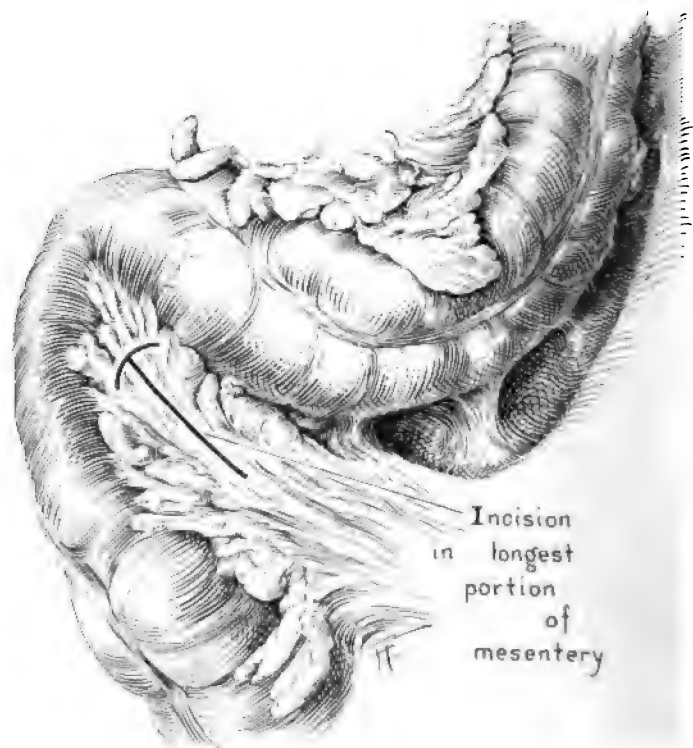
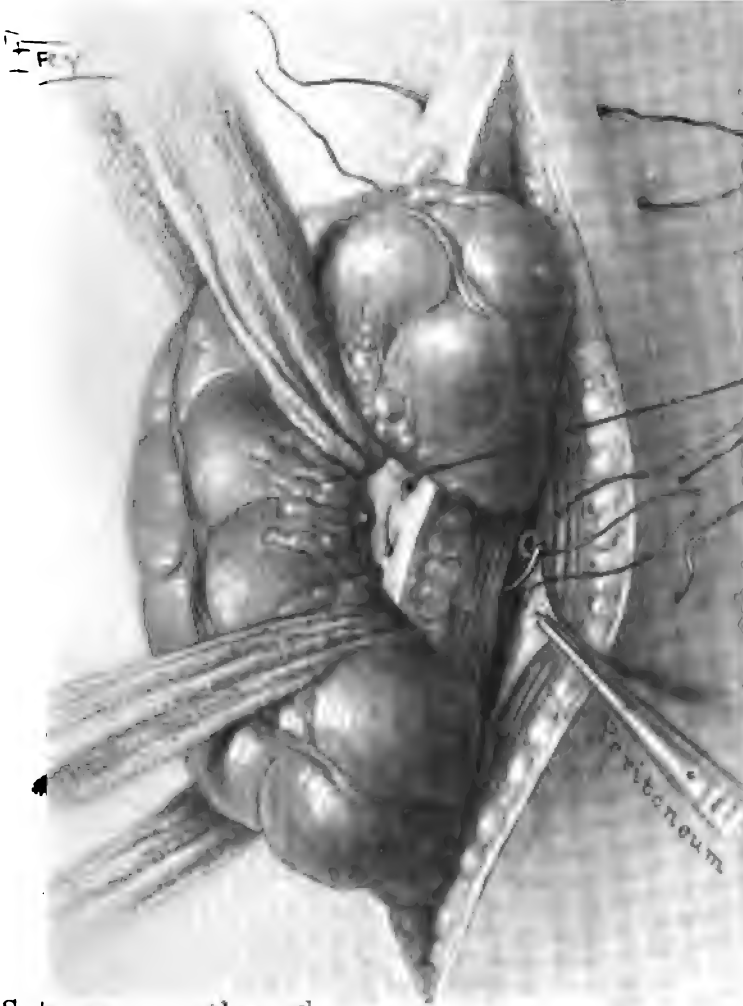


Fig. 85. --Near view of sigmoid flexure, showing the long mesentery in comparison with the short mesentery above it, and also the incision in the mesentery when the sigmoid flexure is used for making a colostomy.

group of colostomies made in this manner it is easy to explain the reasons for the development of most of these conditions. The incision was made over a portion of the bowel which was more or less fixed, and if the sigmoid flexure was pulled up and used as a loop for the colostomy, this was often elevated with considerable difficulty. After the colostomy had been made, the edges of the abdominal wall were separated for a distance of from two to three inches by two limbs of bowel and

the mesentery supplying the loop used for the colostomy. This naturally creates a large opening through the abdominal wall, which in some in-



Sutures pass through  
entire thickness of abdominal wall

Fig. 86.—Edges of the opening in the mesentery of the sigmoid being held widely apart by gauze, while a portion of abdominal wall is being closed through the opening.

stances permitted a herniation of the loop, or allowed the loop to retract or pull inward toward the abdominal cavity.



In many of the operations for excision of the rectum a segment of the sigmoid is left between the colostomy and the site where the bowel



Fig. 87.—Unopened loop of bowel brought out for colostomy after the abdominal incision has been completely closed.

is cut off in making the excision of the rectum. In such instances, if the colostomy retracts sufficiently to permit the distal end to empty its contents into the segment, the feces gradually accumulate and pro-

uce a large painful tumor. Occasionally we have found it necessary ther to remove this segment or to empty it and perform a plastic peration which will more widely separate the ends of bowel.

We are now making a colostomy very similar in type to the one described by Mixer. As a rule, this colostomy is made through a traight incision placed below and about one inch to the left of the umbilicus. An incision of this type possesses distinct advantages. Through it a thorough exploration of the abdominal cavity may be made. If it is found necessary, a primary resection of the bowel is possible, or the first stage of the three-stage Mikulicz operation can be done. The incision may be extended in either direction, and if, after the exploration, it is decided to make a colostomy, this is made through the center or upper end of the incision.

#### OPERATION

The colostomy is made in a loop of the sigmoid flexure; this portion of the bowel is chosen because of its extreme mobility and the length of its mesentery. After the loop has been lifted

out of the abdominal cavity, an incision from one and one-half to two inches in length is made through its mesentery, parallel to the direction of the blood-vessels, and extending upward nearly to the bowel. A second incision, about one inch long, is then made across the end of the first incision, quite near the mesenteric attachment of the bowel. Two strips of gauze are placed in the upper end of this T incision, and when these



Fig. 88.—Ends of the bowel after it has been completely cut across.

are pulled apart, a good-sized opening through the mesentery is created. The two sides of the entire abdominal wall near the center of the abdominal incision are sutured through this opening in the mesentery. The remaining portions of the incision are then closed; a small bite of the bowel is included in two of the sutures to prevent the possibility of herniation of a loop of small intestine. When the gauze has been removed, a glass rod or rubber tube is placed through the opening in the mesentery, between the skin and bowel, to serve later as a guide in cutting across the bowel (Figs. 85, 86, 87, and 88).

If necessary for gas distention, a small opening may be made in the bowel any time after twenty-four to forty-eight hours, and in from five to six days the bowel is cut across completely with the cautery. As a rule, however, the patients pass gases very readily through the knuckle which has been brought up, and it is unnecessary to disturb it before five or six days. After the loop has been cut across it will be found that the two ends of bowel are separated by the entire abdominal wall for a distance of from one to one and one-half inches, and that the cut ends of bowel protrude for a distance of an inch or two above the skin. These may later be cut shorter if thought necessary.

The advantages of an operation of this type can be readily seen. In our hands it has obviated some of the difficulties which have often followed other types of colostomies.

# OME OF THE OLD HOSPITALS OF LONDON, WITH SPECIAL REFERENCE TO THE TREAT- MENT OF FISTULA IN ANO AND HEMOR- RHOIDS\*

W. J. MAYO

After the war the American surgeon will probably go to Germany not seldom for purposes of study as compared to his trips there in former years. It has taken this war, with all its horrors, to give us some idea of the working of the Prussian mind, and we must admit that the German scientific propaganda has been a masterpiece. We have gone to Germany in the past and have seen work which we knew had its origin in America, England, France, Italy, or the Scandinavian countries, appropriated, organized, and exploited without credit to the originators. We have accepted such German exploitations at face value, but the time has arrived when we shall make a new start; we shall resent as never before unfair treatment in scientific discoveries, and shall claim for each country credit for those discoveries which rightly belong to it. Yet the American surgeon must not become provincial. There is so much of interest to be seen abroad that we shall in the future visit many countries instead of confining our time to one, as in the past. We shall become more cosmopolitan and less influenced by German ideas in science, just as we shall free ourselves of the ragged remnants of German ideals.

To the English-speaking surgeon Great Britain offers wonderful scientific advantages. I wish to bear testimony to the honesty and sound sense of the London surgeons—provincial, yes, because in the last generation the English surgeons, as a whole, of whom there have been many charming exceptions, were contented with London, with London methods, with London hospitals, and, too often, with the methods in use in the single hospital in which they served. Shortly before the beginning of the war I had the pleasure of spending some time in London

\* Address in surgery before the Southern Minnesota Medical Association, January, 1919, Mankato. Reprinted from *Minn. Med.*, 1919, ii.

with James Berry, who, besides being one of the most learned and able of the British surgeons, has a deserved reputation as an antiquarian. During the pleasant rambles that I had with him around the limits of the old city of London I learned the why and wherefore of many of her places of historic interest: the reason why sections of the old walled city were given certain descriptive names and why the tower of London, the fortification of William the Conqueror, was placed at one corner of the medieval city so that on one side was the country, on the other the Thames, thus making it impossible for the turbulent city with its unruly inhabitants to surround the home of the king. The fortification was as much against the Londoners as to protect them from armies on the outside.

It is of interest to recall various descriptive words and derivatives of the names of some of the old London institutions; for example, "bedlam" from St. Bethlehem hospital for the insane, founded in 1297. The word grocer, adapted from engrosser, or wholesale dealer, who used the gross weight, dates back to the association of the apothecaries and the grocers who separated in 1617. The apothecaries' guild, handling medicines and articles of light weight and great value, used the Troy pound of 12 ounces.

St. Bartholomew's, a hospital of great traditions, was founded in 1123 and yet is too young to have a place within the walls of the ancient city of London. Guy's Hospital, St. Thomas' Hospital, the London Hospital, and scores of others have been producing centers of medical science and art for hundreds of years.

The Royal College of Surgeons of England, established in 1800, is not so old as the Royal College of Surgeons of Edinburgh, which was founded in 1505 and which signifies its origin by grant from Henry VIII by using the flat cap which he wore as part of their academic uniform. Those marvelous specimens numbered in black, and put up by John Hunter's own hands, which have been exhibited in the museum of the Royal College of Surgeons of London for more than a hundred years, form one of the collections there which has given England one of the foremost positions in the medical sciences for more than a century.

There are many lesser hospitals in London, not so old as those I have named, yet much older than any other hospitals in the world, in which special diseases are treated. The Good Samaritan and the Women's Hospitals are examples which have their counterpart in the various women's hospitals in this country. St. Peter's Hospital, de-

voted to the treatment of stone in the urinary bladder and other urinary diseases, has long been the center of the Urologic School of Surgeons of Great Britain. It is there that Freyer and Thomas Walker work today. The new Brady Hospital in Baltimore, under the able leadership of Hugh H. Young, is the American expression of the same idea in urologic surgery.

Among the most unique and interesting of these pioneer special hospitals, and the only one of the kind with which I am acquainted, is St. Mark's Hospital, founded in 1835, and built for the treatment of fistulas and other diseases of the rectum exclusively. It was here that the great Allinghams, father and son, worked and practised the ligature operation for hemorrhoids. Fistula in ano has been well treated at St. Mark's Hospital for more than forty years. Facts that were known to those working at St. Mark's were apparently given little publicity outside. There have been many different operations for fistula; some of them, especially those used in vesicovaginal fistulas on the general plan of the Whitehead operation, and so ably developed by Elting and C. H. Mayo, have been of great value. But for the "common, every-day" fistula in ano simple successful operations appeared to be forgotten. Any one who has had experience in such cases will remember the humiliation of his own many failures and the number of patients he has seen with incontinence from paralyzed muscles, strictures, and scar tissue lying out along the rectum, all of which were results of surgical interference which not only did not cure, but also left a condition more distressing and more difficult of correction than the original fistula.

Many years ago I was so fortunate as to become acquainted, by personal observation, with the methods introduced in St. Mark's Hospital for the repair of fistula in ano, and as a result I can look back on a most satisfactory experience with this particularly annoying variety of infirmity. Edwards,\* in an interesting communication, credits Goodsall with most important observations regarding fistula in ano. Goodsall states that if a line is drawn transversely through the middle of the anus, all the fistulas lying anterior to that line would pass directly from the external skin opening to the internal opening inside the anal canal, and that all the fistulas posterior to that line would have their internal opening in the midline of the anal canal, posteriorly, no matter where or how many lateral openings, the so-called horseshoe fistulas, are present. In the anterior fistulas, therefore, the external opening will be found opposite

\* Edwards, F. S.: *Fistula in ano*. *Lancet*, 1918, cxcv, 673-674.

the internal opening. An anterior horseshoe fistula, as Edwards remarks, is practically unknown. The cause of the curved or angular shape

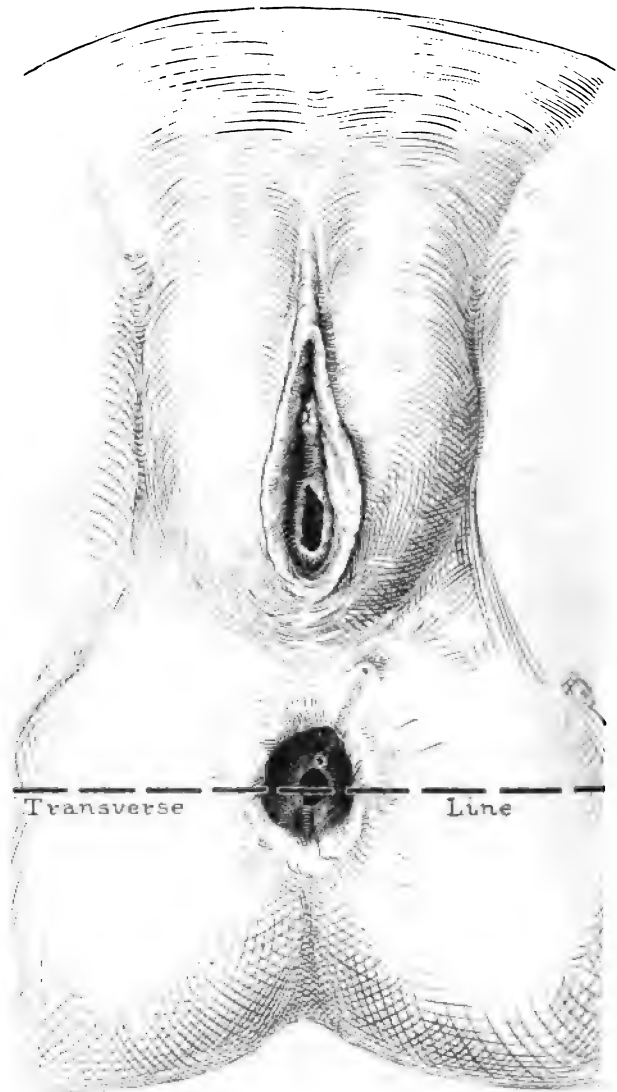


Fig. 89.—Note that fistula lying anterior to the transverse line pass from the cutaneous surface directly to the mucosa.

the posterior fistulas, the external openings of which lie laterally and lead by a crooked passage to the internal opening posteriorly. is the

ngement of the coccygeal ligaments and muscles which protect the  
rnal tissues lying in the midline posteriorly and direct the pus

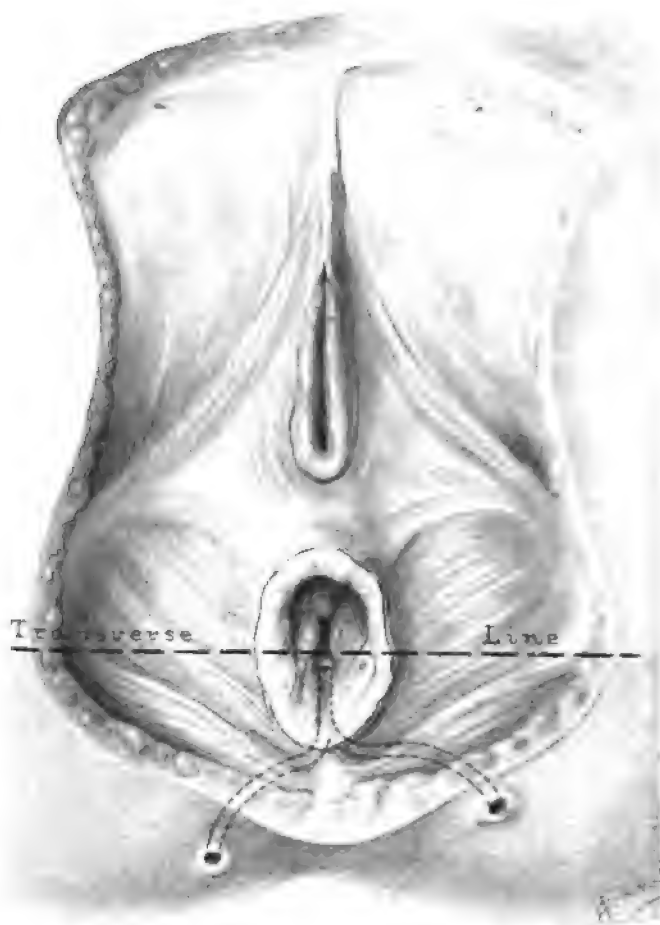


Fig. 90.—Note that there is but one internal opening in the midline posteriorly, although there may be several external openings.

laterally; the so-called horseshoe tracts and openings are thus formed. It is true that one sometimes meets with very superficial fistulas in which the internal and external openings are in the same line poste-



riorly, but in such instances the internal opening is external to the sphincter and just under the mucosa.

The cure of the anterior fistula is quite simple. With the finger in the anal canal and the thumb outside, the induration of the fistulous tract may often be felt. A grooved director may be passed from the external to the internal opening. The tissues, including the muscle, are split through the fistulous tract, thoroughly curetted, and a small piece of iodoform gauze tucked in, so that the trough-shaped opening will be compelled to heal from the bottom. Occasionally I have excised the fistula completely and stitched it up satisfactorily.

The treatment of the posterior fistula, which is the troublesome one, consists of carefully following the one or more external openings to the middle posteriorly, where the fistulous tract leading to the internal opening just above the external sphincter will be readily exposed. This is then split through, and the incisions made by following the lateral fistulous tract are joined. After the use of the curet, if the fistulous tract contains much thick scar tissue, the posterior wall of the tract is split to let the blood supply come through. The tract is dressed similarly to the more simple anterior fistulas, with a strip of gauze which, however, must be replaced once or twice in the case of extensive fistula to insure that no area of granulation tissue becomes buried. It is not necessary to cut the external sphincter more than at one point, and by no means should the mucous membrane of the rectum be split over the pockets lying above the internal opening. These pockets should be gently curetted and a little piece of gauze introduced; this may be removed in forty-eight hours, and no further packing need be used. If the mucous membrane covering these rectal pockets is split, it often leaves a very troublesome sensitiveness, due to the scar tissue.

At King's College Hospital, in 1862, Henry Smith originated the clamp and cautery treatment for hemorrhoids, a method we have used in hundreds of suitable cases with the utmost satisfaction. It is more than twenty years since I found out how to do the clamp and cautery operation properly by reading in the *London Lancet* an acrimonious discussion, carried on between Allingham and Smith. Allingham had misinterpreted the description of the clamp and cautery operation, and, after an experience with it as misinterpreted, he had condemned it. Smith denied being the criminal who had described the operation that Allingham had attributed to him; the only wonder to him was that Allingham had not killed more of his patients. Smith then explained why.

in doing the hemorrhoid operation with the clamp and cautery, the pile should not be trimmed away with the scissors, because, if the eschar pulls apart, the cut artery, which is most resistant, will bleed as Allingham had described; the pile, Smith stated, should be slowly converted into an aseptic eschar, protected by the desiccated tissues, and the bacteria and the hemorrhoid destroyed at the same time. Smith described also how the veins pass downward anteriorly and laterally, so that it is seldom necessary to clamp more than in three places, and stated that there should be a half-inch of sound mucous tissue between each group of vessels destroyed by the cautery in order not to leave a possibility of stricture. Smith also called attention to the technic of stretching the anal muscles; they must be gently stretched and not lacerated or torn in the dilatation, and thus produce nerve injury and scar tissue deposit. The tube and the pack to lead off the gas is unnecessary; as a matter of fact, it had usually been introduced for fear of hemorrhage because the pile had been cut away before being cauterized, rather than for the object ordinarily ascribed to it. Attention was also called to the necessity of not using the clamp and cautery except in operating on internal piles; external piles and tags should be cut away and the skin defect sutured.

An excellent and most satisfactory laxative for use in cases of wounds and injuries about the rectum, such as those following operations, especially for hemorrhoids, was one described by Van Buren in 1866.\*

I trust that this rambling account of a few of the many interesting hospitals of London may help to call to the attention of American surgeons the benefits to be derived from a visit to the medical institutions of the British Isles.

\* *Magnesii sulphatis,*  
*Magnesii carbonatis,*  
*Potassii bitartratis,*  
*Sulphuris loti* .....  $\bar{a}\bar{a}$  ʒj

Sig.—Two drams, more or less, as needed at night, with glass of milk or water.



## **UROGENITAL ORGANS**



## ECTOPIC OR PELVIC KIDNEY\*

E. S. JUDD AND S. W. HARRINGTON

Renal ectopia, or congenital misplacement of the kidney, is a condition in which the kidney has never occupied its normal position; it is to be distinguished from the movable kidney which has wandered from its normal position. Renal ectopia is due to developmental defects of the renal anlage. The renal buds appear on the dorsal aspect of the Wolffian duct, shortly after it has reached the cloaca, as a thickening and bulging of the wall which soon develop into a narrow stalk capped with a mass of mesoblastic tissue designed to be the future kidney. These buds grow dorsally during their process of development, in ascent from in front of the second sacral vertebra, rotate to a lateral position on either side of the vertebral column, and reach their normal position in the lumbar region about the end of the second month. It is not until after they have reached this position that they receive vascularization. This process of ascent and rotation may stop at any point during its course, or it may not be instituted at all; thus the kidney never reaches its normal height and becomes permanently fixed in an abnormal location. Variations in size and form often follow from its adaptation to its surroundings, and are governed to some extent by environment and developmental defects. Often there is an associated defective development of Müller's duct, which does not normally develop until after the primitive kidney has reached its final height, which accounts for the frequent association of genital malformations with ectopic kidney.

Renal malposition is comparatively rare, but occurs often enough to interest diagnosticians, and a sufficient number of such cases develop pathologic conditions requiring surgical intervention, to interest the surgeon. The condition has been recognized for centuries, and was well known to the early writers of the sixteenth century, but it was then of anatomic interest only. Cases were reported by Bauhinus and many

\* Presented before the Southern Surgical Association, Baltimore, December, 1918. Reprinted from *Surg., Gynec. and Obst.*, 1919, xxviii.

others. The frequency of the occurrence of misplaced kidney has been variously stated by different authorities: Naumann, in 1897, reported 21 cases in 10,177 necropsies at the Kiel pathologic institute. Gérard in 1903, estimated its occurrence as 1 in 2500. Guizzetti and Pariset in 1910, reported 18 cases in 20,000 necropsies. Within the last two decades the condition has become of surgical interest, and with the accurate means of diagnosis now used is steadily growing in clinical importance. Dorland, in 1911, reviewed the literature and found 127 clinical cases reported. He stated that about 100 of these had been published since 1898, and that in less than one-third of them the symptoms were due to displacement or disease in the ectopic kidney. Plummer, in 1913, reported 67 cases, collected by Strater in 1906, to which he added 17, making a total of 84 clinical cases. Operations were done in 63 of Strater's 67 cases; 48 were some type of operation on the kidney.

Our series comprises 19 cases of ectopic kidney which have been selected from the records of the clinic. In 9 of these operations were done because of pathologic conditions in the misplaced kidney. In the remaining 10 cases the condition was discovered either during the course of some other operation, or in making a routine examination of the kidney. In these 10 cases the kidney, while misplaced, was not producing any symptoms and apparently was functioning normally.

#### ANATOMIC FEATURES

The ectopic kidney shows some distinct anatomic features, mostly in its blood supply. It is usually approximately normal in size when not diseased, although it may be smaller than normal. It may be oval or pyramidal in contour, depending somewhat on the surrounding structures, and it may retain its fetal lobulations. The origin of the blood-vessels supplying the misplaced kidney is always lower than normal. The arterial supply is very liberal; as many as six vessels entering the kidney have been reported. These vessels may come from the lower few inches of the aorta, from a branch of the aorta, or from both. The usual origin is the lower few inches of the aorta, especially at the bifurcation, but it may be the common iliac, the midsacral or inferior mesenteric. As a rule, the veins correspond to the arterial supply, but an anomalous arrangement is frequently found. The ureter is generally shorter than normal; it usually takes a short tortuous course to the bladder and enters it in the normal position. The pelvis of the kidney and the ureter are usually on the anterior side of the kidney, and in this

manner they retain their fetal relation. The pelvis is not always fully developed. The position that such a kidney assumes varies greatly, depending on the time at which the normal process of development ceases. Its most frequent location is entirely within the small pelvis behind the uterus, to one side, or resting on the promontory of the sacrum or sacro-iliac joint. It is sometimes located in the iliac fossa, and rarely in the abdominal wall. It is usually firmly fixed in the position assumed, due chiefly to its vascular pedicle. It may become movable from trauma or pregnancy. A pelvic kidney is much more frequently found on the left side than on the right, and it is usually on the side where it normally belongs, although crossed ectopic kidneys are quite often seen. Occasionally both kidneys are in the pelvis, and rarely an ectopic supernumerary kidney may be found. The adrenal glands develop independently; they are always found in their normal position and never accompany the ectopic kidney. It is interesting to note the frequency with which genital malformations of both sexes are associated with dystopia of the kidney, particularly in cases of single pelvic kidney. The genital defect, if unilateral, is found on the same side as the ectopic kidney. The more frequent defects are the imperfect development or the entire absence of the uterus and the vagina. There may be an absence of vulvar and urethral openings, and atrophic and undescended testicle is often seen. In quite a number of the reported cases there has also been an imperfect development of the urinary bladder. Definite mental disturbances have been observed to be associated with ectopic kidney, and are believed to be the stigmas of degeneration, due to developmental defects. Ectopic kidneys are usually normal, and although they are subject to all the pathologic conditions to which a normal kidney is subject, they are only discovered by chance during an examination or at necropsy. When any lesion exists in the kidney, there seems to be a tendency for it to become hydronephrotic, probably because of the short ureter and poorly formed pelvis and ureter. The surrounding structures may also play a part in this condition. Stones are frequently found in these kidneys, as is also cystic degeneration and tuberculosis.

#### CLINICAL FEATURES

From clinical observations it appears that pelvic kidney occurs more often in females than in males, but at necropsy it is found as often in the male. This is undoubtedly owing to the fact that the misplaced kidney



in the female is more prone to cause symptoms which simulate disease of the uterus and adnexa, and also menstrual disturbances. When the ectopic kidney is pathologic, the symptoms are the same as when the condition is present in a normally placed kidney. The diagnosis depends on the physical findings, the x-ray, and the kidney examination. The diagnosis, ordinarily, is not easily made, but there are some physical findings which are of aid. The palpation of a tumor through the abdominal wall or rectum, especially with the absence of the kidney from its normal position, is suggestive of the condition. The absolute and relative fixation of the tumor, and often the palpation of the lobulation of a kidney, the depression in the hilus, and at times the pulsation of a large artery on its anterior wall, may be noted. The presence of genital malformation associated with a pelvic tumor should lead one to suspect ectopic kidney. Cystoscopic examination and pyelography give the most accurate data, and it is on these data that a definite diagnosis is made. Frequently the cystoscope reveals certain fairly characteristic features, especially the pulsation in the trigone from an underlying lateral renal artery. The ureteral meatuses are usually normal, but the ureter from the ectopic kidney is much shorter and may be coiled and distorted. The pyelogram shows the abnormal position of the pelvis and makes it possible to determine whether or not the kidney is pathologic. The presence of stones also is shown.

The differential diagnosis is more difficult in the female than in the male, because of the frequency with which the ectopic kidney causes symptoms referable to the adnexa. In many instances a pelvic kidney has been called an ovarian cyst, and explorations have been made with the idea that the condition was a cyst in one of the ovaries. A pyonephrosis in an ectopic kidney has been mistaken for pyosalpinx. The most common error in diagnosis in the male has been in differentiating between the ectopic kidney and inflammation in the appendix. In two of our cases it was quite difficult to determine whether the symptoms were being produced by the appendix which showed a slight degree of inflammation or whether they were produced by some infection in the pelvic kidney.

#### TREATMENT

From a surgical point of view the treatment of ectopic kidney differs in no essential from the treatment when the organ is in its normal position. The mere fact that the kidney did not rise to its normal position

is not indicate that it requires treatment. If the kidney is functioning normally in its malposition, under ordinary circumstances it should be disturbed. A few instances have been reported in which a kidney in the pelvis was interfering with pregnancy, and apparently was the cause of repeated miscarriages. In such cases it might be advisable to attempt to raise the kidney to a higher position. Ordinarily, it is difficult to change the position of the ectopic kidney because the blood-vessels in the pedicle are short and the kidney is rather firmly fixed. In some cases, however, in which the kidney is producing symptoms such



Fig. 91 (154170).—Left ectopic kidney; moderate clubbing and dilatation of calyces. Lead catheter in the right ureter showing the right kidney in normal position.

as would be caused by an intermittent hydronephrosis, although the function may be normal, it would seem advisable to attempt to change its position, and possibly to do a plastic operation at the point of obstruction. This was done in one of our cases, and quite a satisfactory result was obtained. In some of the reported cases in which a nephrorrhaphy had been done it was necessary subsequently to remove the kidney. The problems presented by the ectopic kidney during pregnancy and parturition are often difficult to decide, but fortunately most deliveries are accomplished without surgical intervention. We have not observed

a case of pregnancy complicated in this manner, but from reported cases it would seem that the amount of hindrance to labor depends on the amount of narrowing of the true pelvis, and also on the degree of fixation of the kidney. It has been suggested that if the condition is noted early in the pregnancy, and if it seems to narrow the pelvic inlet sufficiently to hamper labor, an attempt should be made to anchor the kidney above the brim of the pelvis. It has also been suggested that a nephrectomy should be done under such conditions, but we believe that instead of doing a nephrectomy, which might be quite a serious procedure, it would



Fig. 92 (229728).—Solitary right ectopic kidney. Pelvis small and irregular in shape situated opposite base of sacrum. Ureter short and tortuous.

be best to wait until during the last stages of pregnancy, and then perform a cesarean section.

The surgical treatment of pathologic conditions in the ectopic kidney is practically the same as for like conditions in the normally placed organs. In all cases in which there is destruction of kidney tissues, impaired function, and a normal kidney on the opposite side, a nephrectomy is certainly indicated. Before considering nephrectomy in such cases, however, it is very important to determine the condition of the opposite kidney. In three of our cases the ectopic kidney was solitary, and in all it seemed to be the cause of the symptoms.

## REVIEW OF 19 CASES

Nine of the 19 cases of ectopic kidney of this series were operated on for some pathologic condition in the kidney.

In one case an exploration was made to determine the nature of a pelvic tumor, which proved to be a fairly good kidney lying within the pelvis. It was freed from its pelvic attachment and a fixation was made as high up as possible. This seemed to relieve the patient for some time, but she returned in fourteen months with symptoms somewhat the same.



Fig. 93 (225346).—Pelvic outline extending below the crest of the ilium. Right ectopic kidney.

In the second case a diagnosis of a functionless right kidney with hydronephrosis and tumor was made. An exploration revealed an ectopic kidney. Nephrectomy was done, with satisfactory recovery.

In the third case the patient gave a history of gallbladder trouble. Physical examination revealed a rather firm mass in the right abdomen, and exploration showed the mass to be an ectopic kidney, which was freed and fixed in a higher position. The condition of the gallbladder was remedied at the same time. This patient's convalescence was uneventful.

In the fourth case the patient complained chiefly of female trouble,

namely, attacks of pelvic pain on either side which required rest in bed for several days at a time. Examination showed a small mass in the left iliac fossa and a deformity of the vagina and uterus. At operation a pyonephrotic left kidney was found. The ureter was about three inches long, and there were three renal arteries, all coming from the common iliac. The kidney was removed. Convalescence was satisfactory except for a phlebitis in one of the saphenous veins.

In the fifth case the complaint was kidney trouble. Bacilli of tuberculosis had previously been found in the urine, and a diagnosis of



Fig. 94 (17834).—Left ectopic kidney obstruction to left ureter just outside the bladder.

tuberculosis of the right kidney was made. At operation the kidney was definitely tuberculous and was situated in the right iliac fossa. The blood supply came from three large vessels from the lower aorta.

In the sixth case the complaint was of frequent and painful micturition and a cystocele. The cystoscopic examination showed a pyonephrosis on the right side. The combined functional test was only 35 per cent in two hours. At operation a small kidney was found lying in the pelvis, with a hydronephrosis and some infection. The ureteropelvic juncture was a definite stricture which was incised and a plastic operation done. The convalescence was satisfactory.

In the seventh case the chief complaint was left lower abdominal pain. The physical examination was negative, with the exception of tenderness in this region. Obstruction was encountered 10 cm. up the left ureter, and a pyelogram showed that the left kidney was lying in the pelvis and that the pelvis of the kidney and the calyces were dilated. The arterial and venous blood supply was characteristic of an ectopic kidney. A nephrectomy was done and the patient made a good recovery.

In the eighth case the patient complained of a combined urinary and



Fig. 95 (184087).—Left ectopic kidney with moderate hydronephrosis.

fecal fistula in the left inguinal region. The fistula had persisted since an operation for the drainage of a large abscess in this region some weeks previously. Soon after drainage was established stones, urine, and feces began to discharge. Examination revealed an obstruction of the ureter, and x-ray examination showed multiple stones in the pelvis and calyces of a pelvic kidney. Two subcapsular operations were performed; the infected kidney tissues and a large number of stones were removed.

In the ninth case the patient had complained of pain through the pelvis, and a left hydronephrotic pelvic kidney was discovered during

an exploration. The diseased kidney was removed, and the patient made a good recovery.

In one case an exploration was made which revealed an absence of the right kidney and a congenital malformation of the liver and duodenum. The left kidney was large and was situated in the region of the sacro-iliac joint. Fortunately, the absence of the opposite kidney was discovered before anything had been done to the pelvic kidney.

In four of the series the condition of congenital misplacement of the kidney was discovered during the course of some other operation, and



Fig. 93 (151512).—Right ectopic kidney with hydronephrosis.

in most instances the position and condition of the kidney probably had nothing to do with the production of the patient's symptoms. In two cases the kidneys were discovered while an operation was being performed for appendicitis, and in both instances the appendix showed definite inflammation. In view of the fact that the symptoms subsided after the appendix had been removed the position of the kidney apparently had nothing to do with the symptoms. One of these patients, a young married woman, came for consultation because of repeated miscarriages. The pelvic kidney was thought at first to be an ovarian cyst, but on exploration it was found to be a kidney apparently in good

dition. The uterus was lifted up in the pelvis by shortening the ligaments; nothing was done with the kidney. I was unable to get a complete report in this case, so do not know whether the condition was remedied. In one case the pelvic kidney was discovered while an operation was being done for congenital absence of the vagina.

In five cases of the series the malposition of the kidney was discovered on a routine examination by means of a pyelogram. In all of the five cases the kidney was apparently normal with the exception of its position. In two instances the pelvic kidney was found to be a solitary

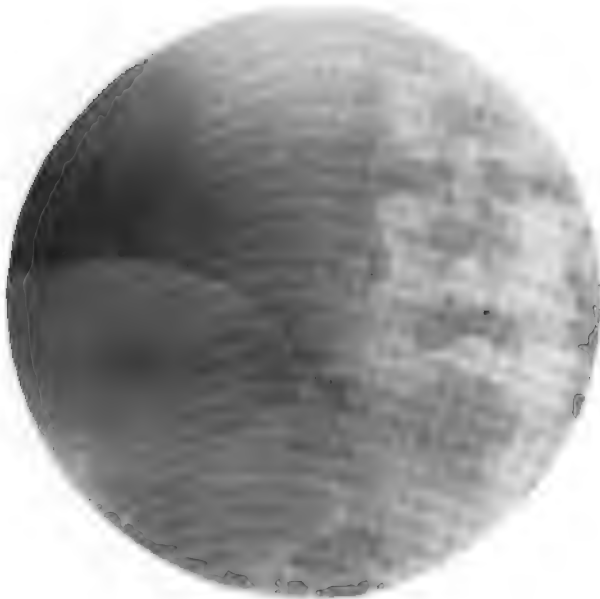


Fig. 97 (120592).—Right ectopic kidney with reduplication of pelvis.

kidney. In one there was lack of development in other regions, and in one there was a reduplication of the pelvis (Figs. 91-98).

#### SUMMARY

In conclusion it may be stated that this particular malposition of the kidney occurs rarely. The kidney may functionate in a perfectly normal manner in this position, and it may never be discovered, or if discovered it will not require treatment. The condition is of interest when the kidney becomes involved in some pathologic process, such as hydro-



nephrosis, pyonephrosis, or tuberculosis. Under these conditions the location of the kidney may be misleading in the diagnosis, which, however, can accurately be made by a careful examination of the bladder, meatus, and kidney by means of the cystoscope, the ureteral catheter.



Fig. 98 (212352).—Left ectopic kidney with pyonephrosis and stones.

and the pyelogram. After the diagnosis has been established the treatment is the same as for a pathologic condition of a kidney in its normal location.

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## RADIOGRAPHIC DIAGNOSIS IN RENAL TUBERCULOSIS\*

W. F. BRAASCH AND F. A. OLSEN

Several articles have appeared in European literature in recent years concerning the value of radiographic findings in the diagnosis of renal tuberculosis. Probably the most comprehensive of these is one written by Burchard, who has made a thorough review of previous literature on the subject. In this country the method has had only limited use, and its importance does not seem to have been appreciated by American observers. Articles referring to the subject have been published by Krotoszyner and by one of the writers (Braasch).

The radiographic data in renal tuberculosis are regarded of such importance at the Mayo Clinic that it is a rule to make a complete radiographic examination of the urinary tract in every case in which renal tuberculosis is suspected. The frequency with which positive data may be obtained in the radiogram is evidenced by the fact that in the years 1916 and 1917, 131 patients were operated on for renal tuberculosis, and radiographic examination of the urinary tract had been made of all. Of this number positive shadows suggestive of renal tuberculosis were found in 30 patients—a percentage of 22. It may be stated, therefore, that approximately one out of five patients with renal tuberculosis will have positive radiographic data of definite diagnostic value, particularly in conditions as follows:

1. When, because of the contracted condition of the bladder or impassable stricture of the ureter, the cystoscopic findings are inadequate.
2. When the cystoscopic findings are not typical of renal tuberculosis.
3. When the clinical findings are not suggestive of renal tuberculosis or of any involvement of the urinary tract, as may occur with a closed tuberculous pyonephrosis.
4. In the presence of bilateral renal tuberculosis, when the typical

\* Paper presented before the Chicago Urological Society, Chicago, April, 1918. Reprinted from Surg., Gynec. and Obst., 1919, xxviii.

shadows frequently render cystoscopy or further clinical examination unnecessary.

The radiographic shadows are caused by the deposit of calcium in the tuberculous area and may assume a variety of forms. To one who has had considerable experience in radiographic interpretation such shadows will have characteristics that are usually recognized. They may be differentiated from a stone shadow: (1) By the variability in its density, as the shadow is irregularly concentrated in different portions; (2) by a shadow of lesser density throughout than that usually observed with stone, and (3) by its irregular and indefinite outline. The calcareous area may, however, simulate the shadow of a renal stone in every particular, and it may be quite impossible to differentiate it without further clinical data. On the other hand, renal stones occasionally cause shadows that are fully as irregular and hazy in outline as a typical tuberculous shadow. It may be said, however, that approximately 75 per cent of tuberculous renal shadows may be recognized as such in the radiogram.

On resection of the kidney an examination of the areas casting shadows in the radiogram will show a considerable variability in the nature of the calcareous deposit. Usually two definite types are recognizable, namely, actual deposits of lime encrusting the ends of the calyces, and caseated areas containing a sufficient deposit of calcium to cast a shadow. Tuberculous shadows may be roughly classified under three groups: (1) Multiple scattered small areas; (2) single or a few localized areas, 1 cm. or more in diameter, and (3) large, irregular, diffuse areas, involving either a large portion or the entire kidney.

In the first group the small scattered areas are generally caused by lime deposits. They are occasionally seen singly, and appear as elongated, irregular, faint streaks, or as multiple punctate areas, scattered over a large portion of the kidney, usually in one of the poles. Unless the renal area in the radiogram is carefully examined, such areas may easily be overlooked.

The second group, representing single or several isolated areas of concentrated calcareous deposit, is the type most easily confused with stone. The shadows are usually of several varieties: (1) A shadow of irregular outline, with a consistence dimmer than that seen with renal stone, and varying in size from 1 to 3 or 4 cm.; (2) a shadow characterized by great irregularity in its consistence and outline, somewhat resembling filigree work, and (3) definite shadows with a density and con-

tour suggestive of stone. The size of the shadow in no way indicates the extent of the tuberculous lesion. A shadow of only a centimeter or two in diameter may be present in a tuberculous lesion involving the entire pole or even the complete kidney.

The third group is characterized by large, regular, rounded shadows of variable density in their various portions. As a rule, on section, the kidney is of a putty-like consistence in the area which causes the shadow. It is, however, impossible to say, from the appearance of such caseated areas, whether or not a shadow will be present in the radiogram. In

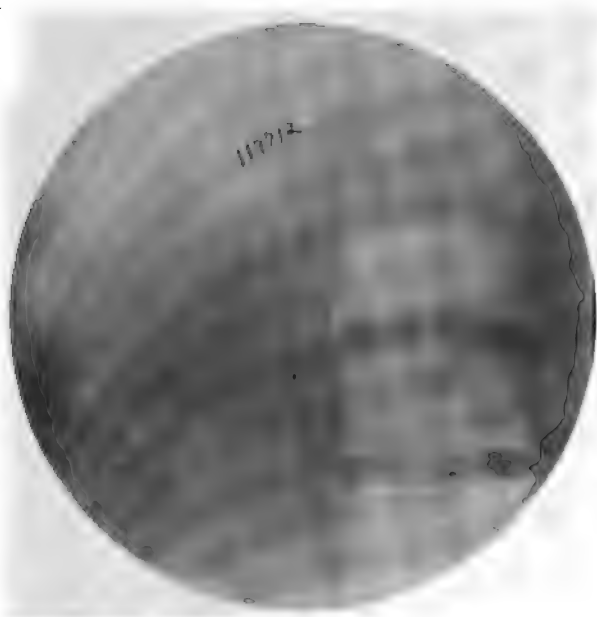


Fig. 99.—Shadows in Group 1 which consist of multiple small calcified areas in the lower pole of the kidney.

two caseated areas of similar appearance one may cast a shadow and the other none at all. Occasionally the calcium deposit is so slight that a soft, diffuse shadow will be seen only on careful plate reading, and it may be easily confused with similar shadows cast by the bowel.

Shadows caused by complete caseation of the kidney are most striking. They may assume the outline of a complete cast of the kidney and are usually irregularly lobulated. The shadow may vary in density in different portions of the kidney, some of which may be so dim as to be scarcely discernible, while others may be definitely and strikingly

outlined. Occasionally, with complete or extensive calcification, the calcium deposit may be so slight that the x-ray simulates that of an attenuated normal renal outline, and it may be difficult to determine whether or not it is an actual pathologic shadow.

Actual renal stone formation is rare in tuberculous kidney. When it does occur, it is generally a phosphatic stone, formed in a localized abscess with necrosis and secondary infection. We have observed this in several cases. Stone formation in the opposite kidney in cases in which a tuberculous kidney had been removed occurred in but two



Fig. 100.—Several calcified areas of larger size with some characteristics of Group 2.

instances that came under our observation. One patient passed a small renal calculus from his remaining kidney two years after the other kidney had been removed for tuberculosis. It may be inferred that primary stone formation is unusual in patients with renal tuberculosis.

*Extrarenal shadows.*—Calcareous deposits of the kidney may be confused with renal stone. They must also be differentiated from various extrarenal shadows which frequently appear in the radiogram. The most common causes of confusion are the deposits in glands situated in the perirenal tissues. Calcified tissues situated in the pleura, sub-

diaphragmatic and retroperitoneal areas are especially likely to cast shadows closely simulating intrarenal calcification. Next to be considered is the possible confusion of shadows caused by substances in the bowel. These may be readily identified, however, by disappearance or change in position while subsequent radiograms are being made. Gall-stones may also occasionally cast a shadow which will closely simulate renal tuberculosis.

*Ureteral shadow.*—Calcareous deposit may occur with tuberculosis in the ureter, although less frequently than in the kidney. When it



Fig. 101.—Single large calcified area in the lower pole of the kidney which belongs to Group 2, suggestive of renal stone.

is present, a considerable portion of the ureter, usually the lower portion, is involved. The shadow may be several centimeters or more in length, and outline the dilated ureter to a greater or less extent. The shadow is caused either by calcareous deposits in the thickened wall of the ureter or by intra-ureteral calcareous deposits. Such deposits are generally accompanied by similar caseation in the kidney. Considerable peri-ureteritis may accompany this calcification of the ureteral wall. The peri-ureteral infiltration, together with the thickened ureter,

will often cause a tumor-mass which can easily be palpated on rectal or vaginal examination. Often calcified glands in the bony pelvis cast shadows suggestive of either stone or tuberculous deposit in the lower ureter. They, however, usually occur with no clinical evidence of tuberculosis in the urinary tract or other portions of the body, and are therefore of no diagnostic significance.

*Calcareous deposits in the prostate gland.*—Occasionally calcium deposits secondary to tuberculosis in the prostate gland cause radiographic shadows suggestive of prostatic stone. Although the clinical findings

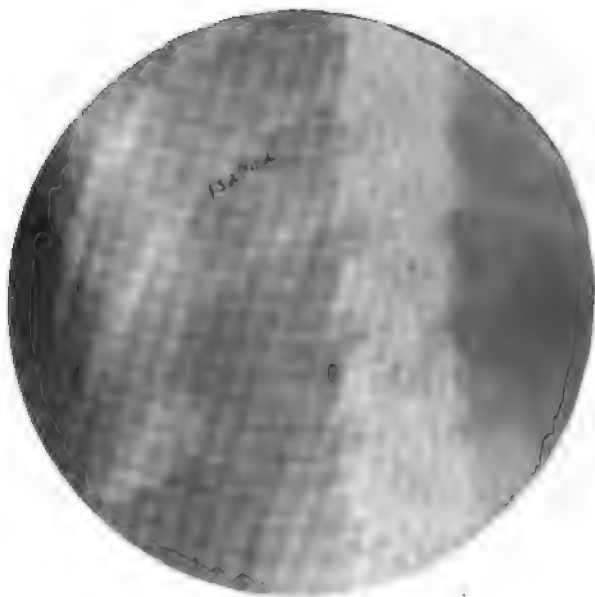


Fig. 102.—Typical "filigree" shadow belonging to Group 2.

should differentiate the two conditions, a chronic healed tuberculous infection may be overlooked.

*Renal outline.*—Interpretation of the outline of the kidney itself in the radiogram is not of much practical value. Some observers have claimed that irregularity of outline of tuberculous kidney may be demonstrated in the unaided radiogram. However, the possibilities of error are so great that these data are not to be relied on. It is well known that bowel contents, the outline of surrounding organs, change in position of the kidney, etc., cause factors which interfere seriously with

accurate interpretation of the renal outline. Occasionally, as Casper has stated, the outline of a greatly hypertrophied kidney on the opposite side of a tuberculous shadow may be of value in indicating hypertrophy subsequent to destruction of the diseased kidney. However, one would be loath to remove a definitely tuberculous kidney without further proof to demonstrate that the hypertrophied kidney is otherwise normal.

*Bilateral involvement.*—Radiographic evidence of renal tuberculosis may be of value in determining the existence of bilateral involvement or that the patient is otherwise inoperable. With shadows of definite tuber-



Fig. 103.—Two areas of calcification of the lower pole with shadows suggestive of stone, Group 2.

culous calcification present in both kidney areas, cystoscopic and further clinical investigation is usually unnecessary. It must be remembered, however, that bilateral renal tuberculosis may exist even though a tuberculous shadow may be found only in one kidney area. This is particularly true with a chronic tuberculous infection in one kidney and a recent involvement of the other. If the bladder is in such a state that it is impossible to make a satisfactory cystoscopic examination, a shadow of calcification in one kidney area might be of considerable diagnostic value. This is illustrated in conditions as follows: (1) When the healthy kidney



crotic process is advanced, it may either assume irregular forms scattered through the parenchyma or it may coalesce to form a large irregular mass.

Occasionally the outline of the necrotic area is apparently detached from the pelvis or connected with it by a narrow isthmus. When the area of necrosis is confined largely to the cortex and is not in direct communication with the pelvis, the pelvic outline may occasionally become contracted in a manner resembling certain forms of pyelonephritis.

As a result of the infective process in the kidney, inflammatory dilatation of the ureter will follow and may be demonstrated in the uretero-



Fig. 106.—Calcified areas in both kidneys, which occurs with bilateral renal tuberculosis.

gram. Should the ureteral mucosa become ulcerated, however, and a stricture ensue, mechanical dilatation may also be present. Ureteral dilatation resulting from tuberculous stricture in the ureter may be confused with that resulting from a benign stricture or obscure lithiasis. If the clinical and cystoscopic findings are insufficient with which to identify the lesion, pyelography will usually demonstrate abnormality in the pelvic outline that is suggestive of tuberculosis.

The cystogram may also occasionally be of diagnostic value. This is particularly true when it is impossible to find either one or both

tus. The bladder outline will be variably contracted, and usually e in one half of the bladder. The demonstration of a dilated ureter making a cystogram with the patient in the Trendelenburg position suggestive of renal involvement on that side. Demonstration of a ely dilated internal bladder sphincter and posterior urethra in the sence of a severe cystitis is also suggestive of tuberculosis.



Fig. 107.- Calcification of the lower portion of a tuberculous ureter.

### CONCLUSIONS

1. The value of radiographic diagnosis of renal tuberculosis does not appear to be fully appreciated.
2. Routine radiography in every case in which there is evidence of infection in the urinary tract is advisable.
3. Shadows may be found in approximately 20 per cent of patients with renal tuberculosis. Such shadows may require the aid of cystoscopic data in their interpretation.
4. Positive evidence of tuberculosis may be obtained by this method when all other clinical data fail, and when cystoscopic examination is impossible.

# THE EFFECT ON THE KIDNEY OF URETERO-VESICAL ANASTOMOSIS. EXPERIMENTAL AND CLINICAL REPORT\*

ANDERS PETERSON

Baker, in 1878, reported a successful implantation of the left ureter into the bladder by operation through the vagina for the relief of incontinence due to the opening of the ureter into the anterior wall of the vagina. McArthur, in 1889, reported a similar case, which he operated on successfully. Davenport, in 1890, implanted an anomalous ureter by the vaginal route, with good results. Bazy, in 1894, reported two instances of ureterovaginal fistula. One patient had an infected hydronephrosis which improved after the implantation of the ureter. Bazy tied a small catheter into the implanted ureter and suggested the use of pelvic lavage with silver nitrate solution 1:500 to 1:100 for infection of the kidney. He also mentions two cases of ureterovesical implantation performed by Novaro, in 1892. Franz, in 1907, published a report of nine experiments on dogs, with excellent results following ureterovesical implantation; also seventeen clinical cases in which four patients were cystoscoped, and the implanted ureter functionated normally. Krönig, in the same year (1907), reported the cases of nine patients operated on for ureteral fistula, following hysterectomy for cancer. His assistant, Rauscher, cystoscoped these patients from five months to one and one-fourth years after the implantation. Good function of the kidney was found in five cases; two showed stenosis and slight hydronephrosis. In two cases of bilateral implantation there was hydronephrosis on the left side and good function on the right side in one, and normal function on both sides in the other.

## TYPES OF TECHNIC

Coffey, in 1911, published a technic for implanting the ureter or the common duct into the intestine. This consists of splitting the serous

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muscular coats for three-fourths of an inch and entering the lumen of the bowel through a small stab wound in the mucosa. The ureter is pulled well into the lumen, by means of an anchoring suture placed

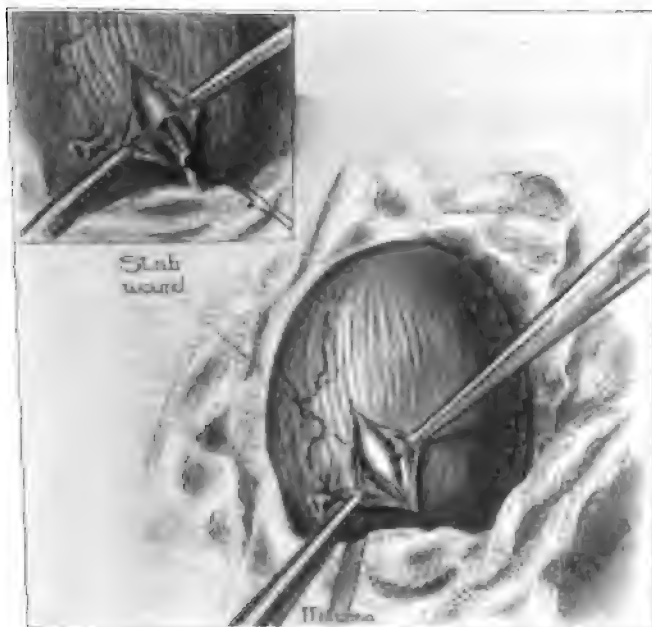


Fig. 110.—Coffey technic employed for implanting the ureter into the bladder; serous and muscular coats split and undermined for embedding of the ureter; split ureter pulled within the cavity of the bladder through the stab wound in the lower angle of the incision.



Fig. 111.—Coffey technic completed, with bladder everted out of the abdomen.

through the split-end of the ureter, and tied three-fourths of an inch below its entrance. The serous and muscular layers are then approximated around the ureter, and one stay suture is placed one-fourth inch above the site of the anastomosis (Figs. 110 and 111).

Stiles' technic consists of entering the lumen of the bowel through a stab wound, and approximating the intestinal wall, without further dissection over the ureter; the wall of the ureter is also caught in these



Fig. 112.—Stab wound through which the ureter is pulled within the cavity of the bladder.

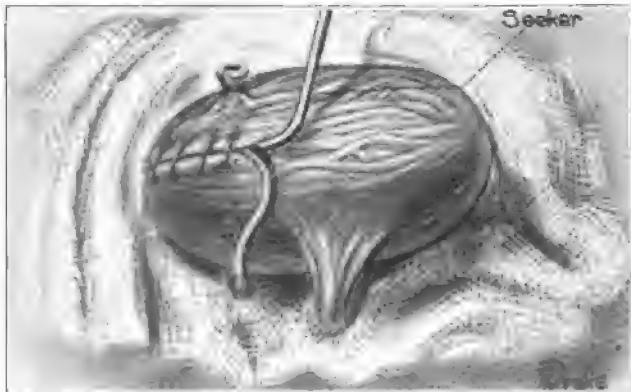


Fig. 113.—Enfolding of the wall of the bladder over the ureter, using a seeker to avoid compression.

sutures. He omits the splitting of the ureter on one side, as well as the stay suture. These methods have been used with slight modifications in our work for implantation into the bladder (Figs. 112 and 113).

Furniss has recently published a simple method of ureterovesical anastomosis, consisting of the penetration of a double fold of the wall

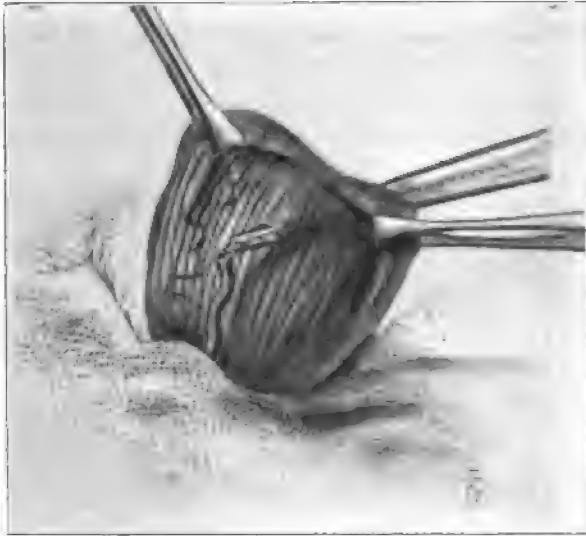


Fig. 114.—The Furniss technic for the implantation of the ureter into the bladder.

of the bladder with an artery forceps, and of the pulling of the severed ureter through both openings made by the forceps. The ureter is secured to the bladder-wall by a few interrupted sutures at its lower entrance into the bladder, and the end is permitted to hang free in the cavity of the bladder. The anterior opening is then closed (Figs. 114 and 115).

A technic suggested by Mann of the Mayo Clinic, a report of which has not heretofore been published, has been used in a few of our experiments. Two parallel incisions, one-fourth inch in length and one-half inch apart, are made at right angles to the long axis of the bladder, extending down to the mucosa. This seromuscular bridge



Fig. 115.—The end of the ureter lies free within the cavity of the bladder.

is undermined, leaving the mucosa intact. A small stab wound is made through the mucosa, at the site of the lower transverse incision. The severed ureter having been split for one-fourth inch on its anterior surface and armed with No. 00 catgut, is pulled beneath the bridge from above downward and anchored to the inner surface of the wall of the bladder one-half inch below the opening. One or two interrupted sutures are made on each side of the ureter, approximating the transverse incision

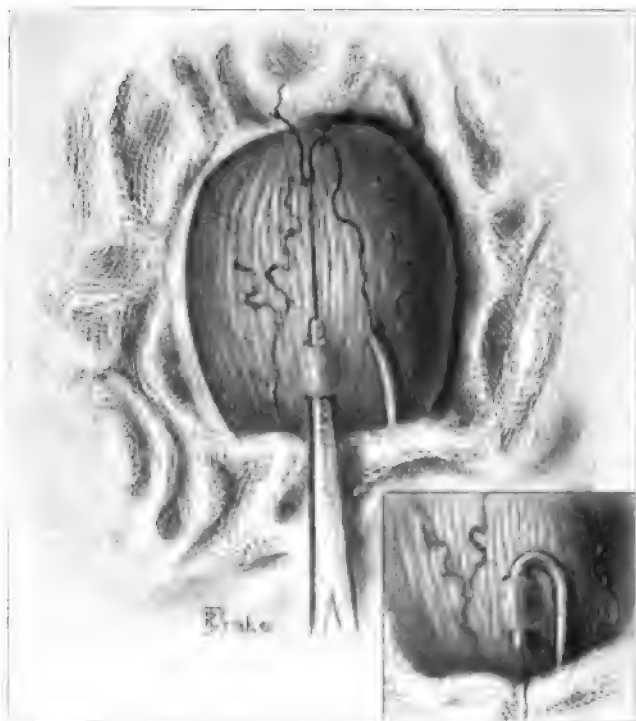


Fig. 116.—Mann's technic for implanting the ureter into the bladder. A seromuscular bridge is undermined, and the ureter is pulled beneath this bridge from above downward.

up to the ureter. No suture is placed into the ureter except the one put through the flap, for the purpose of securing it to the inner side of the wall of the bladder (Figs. 116 and 117).

In making the experimental and clinical observations described in this paper, it has been our purpose to evolve a technic for the re-implantation of the ureter into the bladder, and to study the effect of such operation on the kidney and ureter. Unilateral implantations were

formed on eighteen dogs and bilateral implantations on three, giving total of twenty-four implantations.

Coffey's technic was used in eight cases. Observations of the end results were made from one day to five and one-third months after operation. One animal died from peritonitis on the sixth day. The kidney showed slight hydronephrosis. It was possible to make the ureter leak at the site of anastomosis (Case 1). One death occurred at the end of twenty-four hours. Both ureter and pelvis were dilated, and multiple abscesses were found throughout the kidney. There was also a small localized abscess at the site of the implantation (Case 6). The third animal died from distemper on the tenth day. The pelvis and the ureter both showed a slight hydronephrosis (Case 8). Five animals were examined from three weeks to five and one-third months after



Fig. 117.—Mann's technic of implantation completed, showing the bladder empty and pulled well out of the abdomen.

operation, and showed an entirely normal kidney and ureter. Two observations on the technic were made:

1. In all instances the ureter was implanted on the posterior wall of the bladder a short distance toward the median line of the original insertion, with the bladder pulled well out of the pelvic cavity. It is convenient and natural to imbed the ureter from below upward, but when this is done and the bladder is replaced into the pelvis, an acute angulation in the ureter occurs just at the site of the union with the bladder. If the implantation is reversed, that is from above downward, the ureter will lie in a line with its entrance through the wall of the bladder. In order to have the open side of the ureter facing into the cavity of the bladder, the splitting of the ureter must be done in its anterior wall (Fig. 118).



2. After some observation the last stay suture, placed about a fourth inch above the site of implantation, was omitted, as the implantation is performed with the bladder empty and in a state of contraction. When this viscus becomes distended, a great disproportion occurs between this included section of the ureter and portion of bladder, and the ureter may be acutely kinked and even pulled out of wall of the bladder, as occurred in one of the cases (Case 11, Fig. 115).

Stiles' technic was carried out in 8 cases, with the modification of splitting the anterior aspect of the wall of the ureter for about a fourth inch. No suture, except the anchoring suture, was permitted to enter the wall of the ureter. Care was taken to avoid any injury to the proximal end of the severed ureter, and no forceps was placed on



Fig. 118.—Preparation of the ureter for implantation into the bladder. Anterior wall split from one-fourth to one-half inch, and anchoring sutures introduced.

the end. A forceps was placed on the side of the bladder and the ureter cut with a thin scalpel about 1 cm. above this clamp. While the suture-infolding the ureter in the wall of the bladder were being tied a thyroid needle was used as a seeker in order to avoid any undue compression of the anastomosis (Fig. 113). There were six complete successes in this group of eight operations. In one case (Case 11) the ureter pulled out of the bladder; here the additional stay suture had been used. One animal, sacrificed in a physiologic experiment one and one-third months after operation, showed an advanced pyonephrosis (Exper. 12, Fig. 126).

Five operations were done with the technic devised by Mann. Hydronephrosis resulted in one case four months after the operation. In four cases the kidneys and ureters were normal.

Three implantations were done by the method of Furniss, with nor-

results. One was a bilateral implantation done at one stage; the use of a clamp over the proximal end of the ureter was, however, avoided. The small amount of urine leaking from the ureter in such cases will cause no disturbance unless there is previous infection of the kidney, and then a moist pack placed around the ureter will take care of the trouble.

In order to work out the technic, a cystoscopic examination was made under anesthesia in four normal female dogs and in four dogs whose ureters had been implanted. With the animal in the dorsal position, a small speculum was introduced into the vagina and sufficient

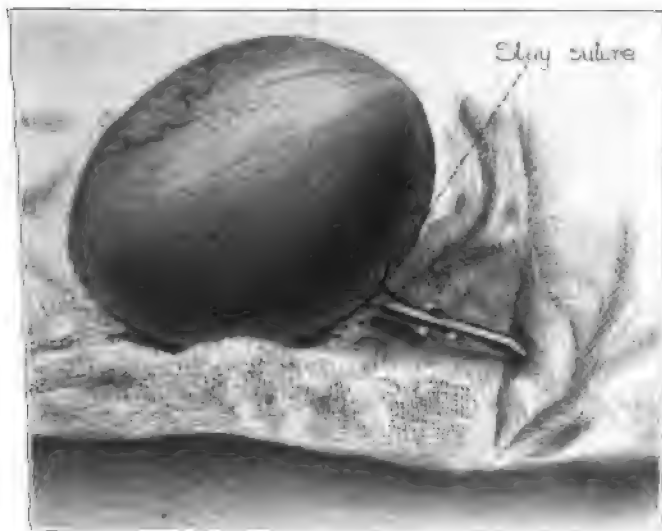


Fig. 119.—Showing tension of the stay suture when the bladder is distended.

traction exerted on the labia to bring the urinary meatus into view from its normal location behind the pubic arch. The cystoscope was then quite readily introduced. The ureters were catheterized with No. 4 or No. 5 ureteral catheters in the normal animals. There was obstruction to the catheter in two of the implanted cases; no obstruction occurred in two.

In the review of the results of the twenty-four experiments, it was found that there were entirely normal kidneys and ureters in fifteen instances; slight hydronephrosis in two; marked hydronephrosis in one; multiple abscesses of the kidney in one; pyonephrosis in one; normal

TABLE 1.—RESULTS OF CYSTOSCOPIC EXAMINATIONS BY VARIOUS FORMS OF TECHNIC

EXPERIMENT NUMBER	Dog	TECHNIC OF TRANSPLANTS				CYSTOSCOPIC EXAMINATION			CAUSE OF DEATH	SACRIFICED IN PHYL. EXP.	NEPHRO-URETERECTOMY	TIME BETWEEN OPERATION AND STUDY OF RESULTS	RESULTS
		Coffey	Stiles	Mann	Furniss	Time after Operation	Obst. to Catheter	No Obst. to Catheter					
1	C152	+	.	.	.	.	.	.	Peritonitis	+	.	6 days	Slight hydronephrosis
2	C153	+	.	.	.	20 days	+	.	.	+	.	5½ mos.	Normal kidney and ureter
3	C154	+	.	.	.	10 days	.	+	.	+	.	5½ mos.	" "
4	C155	+	.	.	.	10 days	.	+	.	+	.	5½ mos.	" "
5	B718	+	.	.	.	.	.	.	Infection of both kidneys	+	.	4½ mos.	" "
6	B502	+	.	.	.	.	.	.	Killed in fight	.	.	1 day	Miliary abscesses in kidney
7	C174	+	.	.	.	.	.	.	Distemper	.	.	3 weeks	Ureter dilated
8	B760	+	.	.	.	.	.	.	.	.	.	10 days	Normal kidney and ureter
9	B779	.	.	.	.	21 days	+	.	.	.	.	4½ mos.	Slight dilatation of kidney and ureter
10	B835	.	+	+	.	.	.	.	.	.	.	4½ mos.	Normal kidney and ureter
11	B666	.	+	+	.	.	.	.	Ureter pulled out	.	.	2 days	" "
12	C220	.	.	+	.	.	.	.	.	+	.	4 mos.	" "
12	C220	.	+	+	.	.	.	.	.	+	.	4 mos.	Hydronephrosis and hydro-ureter. Left
13	B782	.	.	+	.	.	.	.	.	+	.	11½ mos.	Pyonephrosis on right side
14	C227	.	+	+	.	.	.	.	.	+	.	4½ mos.	Normal kidney and ureter
15	C228	.	+	+	.	.	.	.	.	.	.	5 mos.	" "
16	C229	.	+	+	.	.	.	.	Distemper	.	.	1 mo.	" "
17	C268	.	+	+	.	.	.	.	.	.	.	5 mos.	" "
18	C269	.	+	+	.	.	.	.	.	.	.	3½ mos.	" "
19	C276	.	+	+	.	.	.	.	.	.	.	1 mo.	" "
20	C418	.	.	+	.	.	.	.	.	+	.	2½ mos.	Normal kidney. Hypertrophied ureter
20	C418	.	.	.	.	.	.	.	Ureter pulled out	.	.	3 days	Normal kidney and ureter. Left
21	C300	.	.	.	.	.	.	.	Peritonitis	.	.	3 days	Normal kidney and ureter. Right
21	C300	.	.	.	.	.	.	.	.	.	.	1 mo.	Normal right kidney and ureter.

ney and hypertrophied ureter in two, and the ureter pulled out in 3. (Tables 1 and 2.) Fifteen implantations (62.5 per cent) were complete successes. Normally functioning kidneys, including two cases with a slight hydronephrosis, were found in nineteen (80 per cent). There was complete failure from stenosis, infection, and the pulling out of ureters in five cases (20 per cent).

TABLE 2.—SUMMARY

Number of dogs used in experiment.....	21
Number of ureters transplanted.....	24
Coffey's technic of transplantation.....	8
Stiles' technic of transplantation.....	8
Mann's technic of transplantation.....	5
Furniss' technic of transplantation.....	3
Number of dogs cystoscoped.....	4
Obstruction to ureteral catheter.....	2
No obstruction to ureteral catheter.....	2
Death from peritonitis.....	1
Death from pulling out of ureter.....	2
Death from ascending kidney infection.....	1
Death from distemper.....	2
Killed in fight.....	1
Sacrificed in physiologic experiments.....	6
Nephro-ureterectomy.....	7
Exploratory operation for result.....	1
Time elapsing between operation and study of result.....	1 day to 5½ months
Normal kidney and ureter.....	15
Slight hydronephrosis.....	2
Marked hydronephrosis.....	1
Pyonephrosis.....	1
Miliary abscess in kidney.....	1
Normal kidney and hypertrophy of ureter.....	2
Normally functioning kidneys including 2 with slight hydronephrosis (80 per cent).....	19
Failures from obstruction.....	1
Failures from infection (30 per cent).....	2
Ureter pulled out.....	2
Complete successes (62.5 per cent).....	15

Early in these experiments fine silk was used for suture material, and in several instances concretions formed around the sutures in the bladder. This did not occur when catgut alone was used.

It is of interest to note that in two cases (Cases 19 and 21) the kidneys were entirely normal, the ureter was hypertrophied and there was no evidence of dilatation. Partial stenosis takes place at the site of the implantation and the muscularis of the ureter undergoes compensatory hypertrophy, consequently dilatation of the pelvis does not occur until this compensation is overbalanced.

Slight dilatation of the pelvis and ureter was found in two cases (Cases 1 and 8), six and ten days respectively, after implantation. This was probably owing to edema of the lower end of the ureter and of the

wall of the bladder caused by trauma, which subsided in a short time. The utmost care should be taken to minimize trauma during operation.

In view of the end results and the simplicity of the operation, the modification of the Stiles' technic seems the most suitable in ureterovesical anastomosis. The successful outcome of ureterovesical implantation depends entirely on the technic. This consists of: (1) Rigid asepsis to prevent peritonitis and ascending renal infection; (2) a suitable mechanical scheme to establish water proof anastomosis without caus-

ing compression of the ureter; (3) the avoidance of any suture which will enter the wall or lumen of the ureter other than the anchoring suture at its end, and (4) the avoidance of placing any clamp whatever across the extremity of the ureter used in the anastomosis.

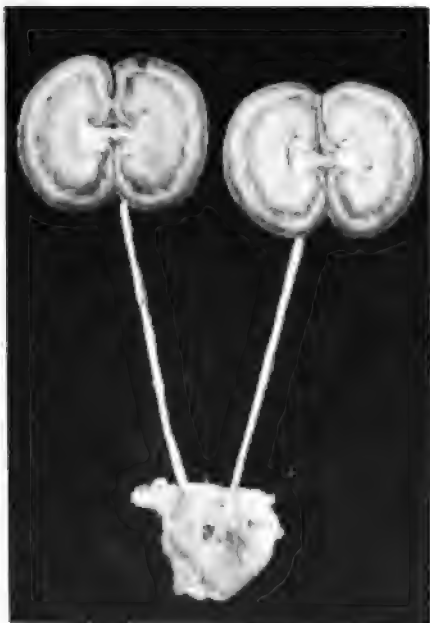


Fig. 120. --Normal kidney and ureter five and one-third months following implantation of the left ureter into the bladder.

#### EIGHT EXPERIMENTS WITH THE COFFEY METHOD

##### EXPERIMENT 1 (Dog C-152).

—Operation Oct. 10, 1917. The left ureter was implanted into the bladder. All sutures through the mucosa were of No. 00 chromic catgut; all other sutures were of silk. The animal did poorly after the operation and died during the night of October 16. Necropsy on the sixth day showed the cause of

death to be infection. The abdominal wound and peritoneum were both badly infected. The left kidney was slightly hydronephrotic. It was possible to make the ureter leak at the site of implantation. The operation was a failure, because of faulty technic.

EXPERIMENT 2 (Dog C-153).—Operation Oct. 10, 1917. Implantation of the left ureter into the bladder. Catgut sutures were used in the mucosa and silk in the serous and muscular coats. On cystoscopic examination under ether anesthesia, Oct. 27, 1917, normal mucous membrane was found. One suture could be seen just above the site of the implantation. Indigocarmin given intravenously appeared on the

at side in eight minutes and on the left in fifteen minutes; a dark color showed on both sides. A No. 5 pointed catheter could be inserted only 5 cm. into the left ureter. Both kidneys drained well. Phenolsulphonaphthalein appeared after six minutes on the right side and after eight minutes on the left. March 21, 1918, the animal was used in a physiologic experiment because it had rheumatism; otherwise it was in good condition. The site of operation was in excellent condition. There were a few adhesions of the uterus to the base of the bladder. Both kidneys and the bladder were removed together. The left kidney and ureter were perfectly normal. On section, both kidneys were found to be exactly alike and perfectly normal grossly, except that in the pelvis of the left organ there was a small, thin calculus. When the bladder was opened, two silk sutures, which were probably the cause of a small calculus near the meatus, were found to be retained at the site of implantation. Microscopic examination showed both kidneys to be practically normal (Fig. 120).

### EXPERIMENT 3 (Dog C-154).

Operation Oct. 17, 1917, implantation of the left ureter. No. 00 twenty-day catgut was used for the closing sutures; fine silk was used for the running suture, and one stay suture of silk was used. Oct. 27, 1917, a cystoscopic examination was made under ether anesthesia. The mucosa of the bladder was normal. The site of the left meatus was slightly above the normal opening

and dilated to twice normal size. A No. 5 pointed catheter was passed easily to the kidney pelvis. Phenolsulphonaphthalein appeared in seven minutes from the catheter. March 27, 1918, the animal was sacrificed in a physiologic experiment and at the end of the experiment a necropsy was made. Both kidneys, the ureters, and bladder were removed intact. The left kidney showed slight dilatation of the pelvis. The ureter was slightly thickened but there was no evident dilatation. The channel through the bladder ran obliquely and admitted a small grooved director easily. The microscopic examination showed the right kidney to be normal. In the left, some of the cells of the tubules were swollen and

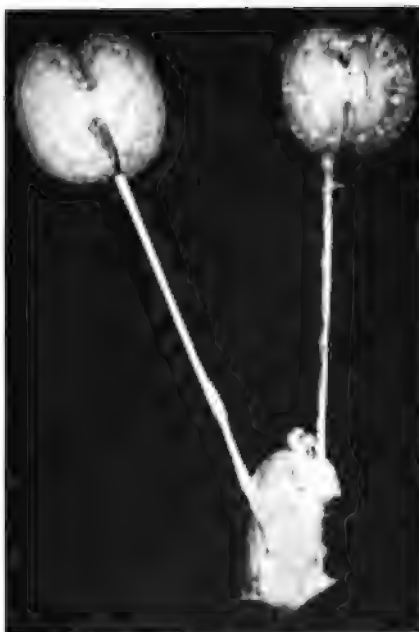


Fig. 121.—Normal left kidney and ureter five and one-third months following implantation of the ureter into the bladder.

some of the tubules were dilated. The glomeruli were slightly congested in the medulla were some rather large abscesses (Fig. 121).

**EXPERIMENT 4 (Dog C-155).**—Operation Oct. 17, 1917. The left ureter was sectioned near the bladder and reimplanted. Oct. 27, 1917, cystoscopic examination showed a small granulating area in the region of the implanted meatus. A No. 5 pointed catheter passed easily to the pelvis of the kidney and indigocarmin appeared in four minutes. March 28, 1918, a left ureteronephrectomy through a median line incision was done. The kidney was normal in size, and there was no dilatation of the capsular veins. The ureter was normal in size. The kidney and



Fig. 122.—Normal kidney and ureter five and one-third months following implantation of the ureter into the bladder.

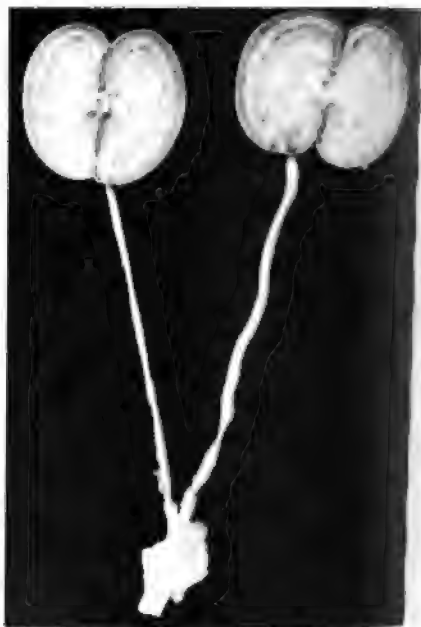


Fig. 123.—Normal kidney and slight hypertrophy of left ureter four and two-thirds months following implantation of the ureter into the bladder.

ureter were split and found entirely normal. Microscopic examination revealed a normal kidney except for some congestion of the glomeruli, which was probably due to the operative manipulations (Fig. 122).

**EXPERIMENT 5 (Dog B-718).**—Operation Oct. 31, 1917. The left ureter was implanted to the median side of the normal opening. No. 00 twenty-day catgut was used throughout. The animal was used in a physiologic experiment March 21, 1918. The site of operation was found in good condition. Both kidneys and the bladder were carefully dissected. The left ureter and kidney were perfectly normal grossly.

The entrance into the bladder was in excellent condition. The operation was a perfect success. Microscopic examination revealed both kidneys to be practically normal (Fig. 123).

**EXPERIMENT 6 (Dog B-502).**—Operation Oct. 31, 1917. Implantation. No. 00 twenty-day catgut was used for all sutures. The dog died during the night of November 1. At necropsy, two stitch abscesses were found in the abdominal wound. The left kidney was enlarged and soft, and the capsular veins were dilated. On section, the organ showed small miliary abscesses throughout. The ureter was dilated and there was a small abscess at the site of implantation. A marked cystitis was present. The right kidney showed slight infection, grossly.

**EXPERIMENT 7 (Dog C-174).**—Operation Oct. 31, 1917. Implantation of the left ureter. Catgut was the only suture material used for the vesical suturing. Nov. 21, 1917, the right ureter was implanted at the median side of the normal opening. The left ureter had been implanted three weeks previously. On inspection no hydronephrosis was found in the left kidney, and the ureter was only slightly thickened. Nov. 23, 1917, the dog was badly mutilated in a fight; a specimen was not obtained.

**EXPERIMENT 8 (Dog B-760).**—Operation Nov. 7, 1917. The left ureter was implanted at the median side of the normal opening. No. 00 twenty-day catgut was used for bladder sutures. The ureter was quite tense when the work was completed. A considerable amount of urine was spilled into the abdomen. The animal developed distemper and died Nov. 17, 1917. At necropsy the left ureter and pelvis of the kidney showed beginning dilatation. The exact site of obstruction was not determined, but it was believed to be at the very end of the implanted ureter. Microscopic examination of the left kidney showed a definite increase in the connective tissue. Many of the tubules were dilated; in other tubules the cells were swollen. There were a few small areas of round-cell infiltration. On the whole, the organ appeared badly damaged.



Fig. 124.—Normal kidney and ureter four and one-half months following implantation of the ureter into the bladder.

#### SIXTEEN EXPERIMENTS BY THE STILES, MANN, FURNISS, AND COFFEY TECHNIQS

**EXPERIMENT 9 (Dog B-779).**—Operation Nov. 7, 1917. Implantation of the left ureter into the bladder (Mann's technic). Cystoscopic



examination Nov. 29, 1917, showed the bladder mucosa normal and left meatus surrounded with granulation tissue. The left ureter could not be catheterized because of the location of the meatus, as well as the reaction following the operation. March 20, 1918, a left nephro-ureterectomy was done through a left rectus incision. The kidney and ureter were normal in size and appearance. The animal was pregnant. Microscopically the kidney appeared normal except for the slight dilatation of some of the tubules (Fig. 124).

**EXPERIMENT 10 (Dog B-833).**—Operation Nov. 7, 1917. Re-implantation of the left ureter (Mann's technic). Cystoscopic examination, Nov. 29, 1917, showed normal mucosa. The site of the anastomosis was clean. A catheter could not be passed up the ureter. March 27, 1918, a left nephro-ureterectomy was done through a left rectus incision. The kidney was normal in size and appearance. The ureter was slightly thickened, but no dilatation was seen. Microscopically the kidney was normal (Fig. 125).



Fig. 125.—Normal kidney and ureter four and two-thirds months following implantation of the ureter into the bladder.

**EXPERIMENT 11 (Dog B-666).**—Operation Nov. 14, 1917. The right ureter was implanted to the median side of the normal opening (Stiles' technic). The left ureter had previously been implanted in the sigmoid, and was dilated almost to the size of the intestine. The animal died two days after operation. The abdomen contained 500 c.c. of fluid, which proved to be urine. There had been leakage at the site of implantation. This appeared to be due to the last stay suture which had cut through the ureter and pulled the end of the ureter from the bladder.

**EXPERIMENT 12 (Dog C-220).**—Operation Nov. 14, 1917. The left ureter was implanted to the midline of the normal site by the Mann technic; no outer stay suture was used. Jan. 30, 1918, the right ureter was implanted into the bladder by Stiles' technic. The left ureter was found to be dilated to three times the normal size. The kidney was only slightly dilated. March 8, 1918, the animal was used in a physiologic experiment. The left kidney and ureter were dilated to twice the normal size; there was partial stenosis at the bladder junction. The pelvis of the kidney contained clear fluid. The right kidney was three times its normal size; the right ureter twice its normal size. There was complete stricture at the wall of the bladder. The kidney was filled with pus. On

scopic examination, the histologic picture of the right kidney was better than the gross picture. There was a definite amount of reabsorption of urine done to the left kidney, which was almost completely destroyed (Fig. 126).

**EXPERIMENT 13 (Dog B-782).**—Operation Nov. 14, 1917, implantation of the left ureter (Mann's technic). March 20, 1918, a left nephrectomy was done through a left rectus incision. The left kidney the junction of the ureter and bladder were found entirely normal in appearance. Microscopic examination showed this kidney to be histologically normal (Fig. 127).

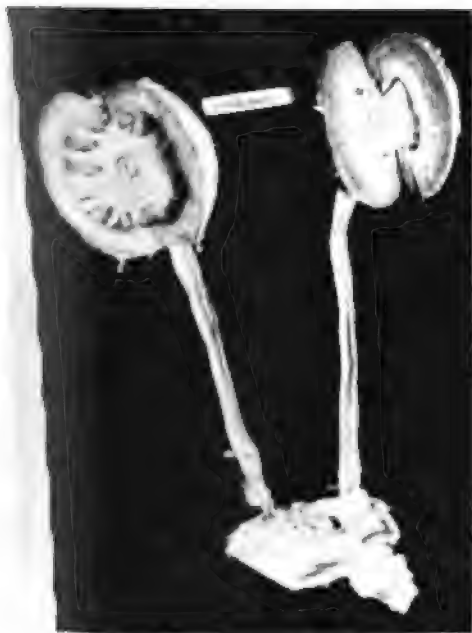


Fig. 126.—Section of specimen showing partial stenosis with hydronephrosis on left and complete stenosis with advanced dilatation on right.



Fig. 127.—Normal kidney and ureter four and one-quarter months following implantation of the ureter into the bladder.

**EXPERIMENT 14 (Dog C-227).**—Operation Nov. 21, 1917. Stiles' implantation of the left ureter. April 17, 1918, a left nephro-ureterectomy was performed. There was no evidence of change in either the kidney or the ureter. Microscopically the organ appeared to be practically normal (Fig. 128).

**EXPERIMENT 15 (Dog C-228).**—Operation Nov. 21, 1917. Implantation of the left ureter (Stiles' technic). The animal developed distemper shortly after the operation, and died Dec. 23, 1917. Necropsy

showed the characteristic lesions of distemper. The operative wounds were completely healed. The left kidney was slightly smaller than the right. The left ureter was normal. Microscopic examination of the left kidney showed a definite increase in the connective tissue of this organ. Many of the tubules were completely isolated. Cells of some of the tubules were swollen. In the cortex there were areas of round-cell infiltration.

**EXPERIMENT 16 (Dog C-229).**—Operation Nov. 21, 1917. Implantation of the left ureter by Stiles' technic. Jan. 23, 1918, an explora-



Fig. 128.—Normal kidney and ureter five months following implantation of the ureter into the bladder.



Fig. 129.—Normal kidney and ureter on left five months after implantation into the bladder and normal result on right three months following implantation into sigmoid. Specimen reversed in photo.

tion was made. The site of implantation was in good condition and the left kidney and ureter appeared normal. The right ureter was implanted into the sigmoid by the Coffey technic. April 17, 1918, both ureters with a section of the bladder on the left side and a portion of the bowel into which the right ureter had been implanted were removed. There was no dilatation of either ureter, and both kidneys were normal (Fig. 129).

**EXPERIMENT 17 (Dog C-268).**—Operation Jan. 8, 1918. The left ureter was implanted into the bladder (Stiles' technic). April 17, 1918,

the left kidney and ureter were removed, together with a section of the bladder. No evidence of dilatation was found (Fig. 130).

**EXPERIMENT 18 (Dog C-269).**—Operation Jan. 9, 1918. Implantation of the left ureter by the Stiles technic. Feb. 9, 1918, implantation of the right ureter into the sigmoid by the Coffey technic. There was no evidence of dilatation of the left kidney or ureter. The animal died suddenly two days after the last operation, due to a gross infection from the bowel. The left kidney and ureter were normal. Microscopic



Fig. 130.—Normal kidney and ureter three and one-third months following implantation of the ureter into the bladder.

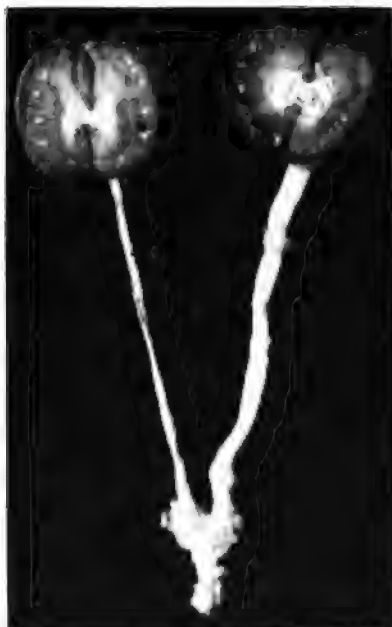


Fig. 131.—Normal kidney and hypertrophied ureter two and one-third months following implantation of the ureter into the bladder (left side).

examination of the left kidney showed a normal organ except for some very small abscesses in the pelvic mucosa.

**EXPERIMENT 19 (Dog C-276).**—Operation Jan. 9, 1918. Implantation of the left ureter (Stiles' technic). March 18, 1918, the dog was sacrificed in a physiologic experiment on account of having distemper. At necropsy the union of the left ureter in the bladder was found to be firm. A No. 5 catheter passed easily through the anastomosis. The ureter was hypertrophied to twice its normal size, but there was no evidence of dilatation of the pelvis of the left kidney. Microscopic examination of the left kidney showed a few scattered areas of round-

cell infiltration and some dilatation of the tubules. Otherwise the organ was normal (Fig. 131).

**EXPERIMENT 20 (Dog C-418).—**Operation April 10, 1918. The left ureter was implanted into the bladder by the Mann technic, and the right was implanted by the Furniss technic. The dog refused both food and water, and died on the third day. At necropsy, about 200 c.c. of purulent fluid was found in the abdomen. The site of anastomosis of the right ureter was firm; the left had pulled completely out of the bladder. There was no dilatation of the kidneys or the ureters, and no gross evidence of infection in the kidneys or at the site of anastomosis.

**EXPERIMENT 21 (Dog C-400).—**Operation April 3, 1918. Bilateral implantation of the ureters into the bladder by Furniss technic. May 8, 1918, an exploratory operation was done to enable the operator to study the result. Both kidneys were normal in size and appearance; the left ureter was slightly thickened, and the right normal in size.

#### CLINICAL REPORT

In twenty-one cases in the Mayo Clinic the ureter has been implanted into the bladder and the effect on the kidney has been noted. Fifteen patients had extensive resections for tumor of the bladder, and implantation of one ureter; four had ureterovaginal fistula; in one the right ureter opened into the urethra, and in one the left ureter opened into a diverticulum.

The patients who were operated on for malignancy and returned for examination have been longest under observation, three for four years, and eight for from three months to one year. When implantation was done for conditions other than tumor of the bladder, the time elapsing between the operation and the cystoscopic examination varied from eighteen days to four months. The cystoscopic examination consisted of a careful inspection of the entire bladder. The condition of the implanted meatus as to size and contractions, and the appearance of the excretion were noted. Whenever feasible both ureters were catheterized and a differential functional test with phenolsulphone-phthalein was done followed by a pyelogram of the implanted side. In the cases in which the implanted ureter could not be catheterized, a Garceau catheter was passed well up on the normal side, urine from the bladder was taken from the implanted side and a differential test made. When neither side was catheterized indigocarmin was given intravenously, and the time of its appearance and the intensity of the color as it appeared at the meatus were noted (Tables 3 and 4).

TABLE 1.

TABLE 9.																	
NUMBER	DIAGNOSIS	TIME FROM OPERATION AND CYSTOSCOPIC EXAMINATION	SIDE TRANSPLANTED	CYSTOSCOPIC EXAMINATION					FUNCTIONAL TESTS					PYELOGRAM		REMARKS	
				Dilated Mucosa	Contracted Mucosa	Urinary Spouting	No Obstruction to Catheter	Obstruction to Catheter	Microscopic Examination of Urine for Pus	Appearance of Indigo-carmin	Appearance of Phthalein	Per cent Output Phthalein	Normal	Dilated			
I.	1 (80914)	Bladder tumor	4 1/2 yrs.	Rt.	+	+	+	+	+	1	..	..	15	17.5	..	..	Normal kidney, four and one-half years.
	2 (86191)	Bladder tumor	4 1/2 yrs.	Rt.	+	+	+	+	+	1	..	..	20	16	..	..	Normal kidney, four and one-half years.
	3 (100111)	Bladder tumor	4 yrs.	Rt.	+	+	+	+	+	0	..	..	9	17.5	+	+	Small hydronephrosis, four years.
	4 (163712)	Bladder tumor	1 yr.	Rt.	+	+	+	+	+	..	..	..	15	Tr.	+	..	Normal kidney, one year.
	5 (185582)	Bladder tumor	10 mos.	Lt.	Not seen	+	+	+	+	..	..	..	12	..	..	..	Functionless kidney, ten months.
	6 (69925)	Bladder tumor	8 mos.	Lt.	Not seen	+	+	+	+	..	..	..	..	..	..	..	Normal spurs seen from left meatus. Eight months.
	7 (186610)	Bladder tumor	7 mos.	Lt.	+	+	+	+	+	1	..	..	4	20	..	..	Normal kidney, seven months.
	8 (213632)	Bladder tumor	4 mos.	Lt.	+	+	+	+	+	0	5 min.	..	..	2	..	..	Normal kidney, four months, twenty-two days.
	9 (213837)	Bladder tumor	4 mos.	Lt.	+	+	+	+	+	..	None in 15 min.	..	25	9	..	..	Functionless kidney, four months.
	10 (213710)	Bladder tumor	4 mos.	Rt.	+	+	+	+	+	..	..	..	..	..	..	..	Functionless kidney, four months.
	11 (204790)	Bladder tumor	3 mos.	Lt.	Not seen	+	+	+	+	..	..	..	12.5	17.5	..	..	Normal kidney, three months.
II.	12 (221950)	Ureterovaginal fistula	1 mo.	Lt.	Not seen	+	+	+	+	..	None in 15 min.	20	..	0	..	..	Functionless kidney, one month.
	13 (214196)	Ureterovaginal fistula	7 wks.	Lt.	Not seen	+	+	+	+	3	5 min.	..	..	..	+	..	Normal kidney outline and function seven weeks.
	14 (102891)	Ureterovaginal fistula	18 das.	Lt.	Not seen	+	+	+	+	4	..	..	..	..	..	..	Infected hydronephrosis, eighteen days.
	15 (144658)	Ureterovaginal fistula	20 das.	Rt.	..	+	+	+	+	..	..	..	13	9	..	..	Functionless kidney, twenty days.
	III.	16 (163925)	Right ureter opening into urethra	4 mos.	Rt.	+	+	+	+	+	4	..	15	..	30	..	..
17 (215976)		Left ureter opening into diverticulum	6 wks.	Lt.	Not seen	+	+	+	+	..	..	..	25	12	..	..	Fair function six weeks.

combined output is normal, or nearly normal, and a widely dilated ureter is found, it is safe to assume that the normal phenolsulphonephthalein output is from the opposite side, and ligation of the ureter may be safely done.

In all cases in which advanced pathologic changes of the kidney and ureter have not occurred prior to surgical relief, and in which tension can be avoided, the reimplantation of the ureter into the bladder should be done.

### CONCLUSIONS

1. From experimental and clinical observations it is obvious that a normal or almost normal kidney and ureter should result following the implantation of the ureter into the bladder.

2. The utmost care to minimize the operative trauma must be observed.

3. The placing of a forceps over the end of the ureter should be avoided.

4. No suture should enter the wall or lumen of the ureter other than the anchoring suture placed in the split extremity of the ureter; and the approximation of the wall of the bladder must be accomplished without undue compression.

5. When marked dilatation of the ureter has occurred prior to surgical interference, and when it is necessary to implant the ureter under tension, a successful result is very doubtful and ligation is preferable to any effort of implantation.

### REPORT OF CASES

CASE 1 (80914).—A woman, aged forty years, was admitted to the clinic March 4, 1913. A diagnosis was made of a broad, flat carcinoma extending over the base of the bladder and into the urethra. Aug. 6, 1913, excision and cautery of the base of the tumor and implantation of the right ureter were done. The patient returned each year for cystoscopic examination. There was no recurrence except a persistent carcinoma of the urethra, which was cauterized; microscopic examination showed it to be inflammatory. Oct. 26, 1917, four and one-fourth years after the resection of the growth, the left ureter was catheterized. The differential functional phenolsulphonephthalein test showed 15 per cent from the ureter, and 17.5 per cent from the bladder specimen in fifteen minutes after intravenous injection. Nov. 30, 1917, the right ureter was catheterized easily, and clear urine flowed normally through the catheter. A pyelogram made on this date showed no dilatation of the pelvis (Fig. 132). The patient is in good general condition.

**CASE 2 (86197).**—A woman, aged fifty years, was admitted to the clinic June 18, 1913. A diagnosis of malignant papilloma of the base of the bladder was made. June 25, 1913, suprapubic resection of the right quadrant and floor of the bladder with implantation of the right ureter was done. Cystoscopic examinations in 1914, 1915, 1916, and 1917 showed no evidence of recurrence. Feb. 8, 1918, four years and one-half months after the removal of the tumor, a dilated ureteric meatus was found. The catheter could not be passed up the ureter. The left ureter was catheterized with a Garceau catheter. An intravenous phenolsulphonephthalein test showed 20 per cent excretion in the ureter, and 15 per cent in the bladder in fifteen minutes. The patient's general health is good.



Fig. 132.—Pyelogram showing normal kidney pelvis four years following implantation of ureter into the bladder.



Fig. 133.—Pyelogram showing hydronephrosis four years following the implantation of the ureter into the bladder.

**CASE 3 (10011).**—A man, aged fifty-three years, was admitted to the clinic Feb. 4, 1914. A suprapubic resection of a tumor of the bladder had been done elsewhere about six months previous to admission. A recurring tumor of the bladder was found, and Feb. 7, 1914, resection and cauterization of one-half of the bladder with implantation of the right ureter was done. Nov. 5, 1914, cauterization of the bladder for recurrence was again necessary. Cystoscopic examinations in 1915, 1916, and 1917 showed a small recurring growth at the site of the operation scar, which was fulgurated. Examination Dec. 4, 1917, showed a small reddened area in the old scar but no evidence of recurrence. The right ureteric opening was widely dilated, and frequent spurts of urine came from



the meatus. The secretion from the right ureter showed a few cells. The phenolsulphonephthalein test showed 4 per cent in the right ureter and 5 per cent in the left in fifteen minutes. A pyelogram of the right kidney showed a small hydronephrosis. The patient is in excellent health (Fig. 133).

**CASE 4 (163712).**—A man, aged sixty-nine years, was admitted to the clinic June 23, 1916. A diagnosis was made of a papilloma of the bladder the size of a hen's egg, lying in the right base. July 11, 1916



Fig. 134.—Normal pyelogram of the right kidney one year following the implantation of the ureter into the bladder.

excision of the tumor and implantation of the right ureter was done. Papillary epithelioma was diagnosed pathologically. A cystoscopic examination Oct. 27, 1917 one year and three and one-half months after operation showed no recurrence. The catheter passed easily up the right ureter and negative urine was collected. Phenolsulphonephthalein output showed 15 per cent in the right ureter, and 17.5 per cent in the bladder. The pyelogram showed the right kidney to be normal.

The general condition of the patient was good (Fig. 134).

**CASE 5 (185582).**—A woman, aged sixty years, was admitted to the clinic Feb. 13, 1917, and a diagnosis of carcinoma of the bladder was made. March 21, 1917, a suprapubic excision of one-third of the wall of the bladder was done. One inch of the right ureter was removed and the left ureter was implanted into the base of the bladder. It was not possible satisfactorily to reconstruct the bladder. The involved portion of the urethra was removed also. Jan. 22, 1918, ten months after the operation, there was no evidence of recurrence of the tumor. The left meatus could not be seen; the right was normal. A catheter was passed well up the right ureter. The phenolsulphonephthalein output showed 12 per cent in the right ureter, and a trace in the bladder.

fteen minutes. The left kidney was found to be functionless, probably because of the tension on the ureter necessary for its implantation.

**CASE 6 (69825).**—A man, aged fifty-four years, was admitted to clinic June 27, 1912. A carcinoma of the left base and wall of the bladder was found. July 6, 1912, suprapubic resection of one-third of bladder with cautery of the base, and implantation of the left ureter, was done. Cystoscopic examination March 8, 1913, showed no evidence of recurrence. The left meatus spurted urine normally. In answer to inquiry in August, 1916, the patient stated that he was in good health and had no urinary inconvenience.

**CASE 7 (186610).**—A man, aged fifty-four years, was admitted to clinic Feb. 23, 1917. March 9, 1917, suprapubic resection of one-third of the left wall of the bladder and one-half of the left ureter, with implantation of the ureter, was done for carcinoma. Oct. 18, 1917, cystoscopic examination showed no recurrence. The left meatus was widely open and spurted urine normally. A catheter passed easily and the specimen of urine showed a few pus-cells. Intravenous phenolsulphonephthalein appeared in four minutes, from the left ureter 4 per cent, and from the bladder 20 per cent. The catheter drained poorly. The pyelogram showed a normal kidney and ureter (Fig. 135). The patient's health is good.



Fig. 135.—Normal pyelogram of the left kidney seven months following the implantation of the ureter into the bladder.

**CASE 8 (213632).**—A man, aged forty-eight years, was admitted to the clinic Nov. 20, 1917. A suprapubic excision with cautery was done at the base of the left wall of the bladder and base of the left ureter for multiple papilloma. One large growth the size of an orange was situated at the left meatus. Cystoscopic examination four months and twenty-two days after the operation showed no evidence of recurrence. The left meatus, which was located high up on the left wall of the bladder, was catheterized easily. Indigocarmine, dark blue in color, appeared in five minutes on both sides. The pyelo-ureterogram showed a normal pelvis and ureter throughout. Examination of urine from the left kidney was negative (Fig. 136). The patient has gained 8 pounds in weight and has no urinary inconvenience.

the meatus. The secretion from the right ureter showed a few pus-cells. The phenolsulphonephthalein test showed 4 per cent in the right ureter and 5 per cent in the left in fifteen minutes. A pyelogram of the right kidney showed a small hydronephrosis. The patient is in excellent health (Fig. 133).

**CASE 4 (163712).**—A man, aged sixty-nine years, was admitted to the clinic June 23, 1916. A diagnosis was made of a papilloma of the bladder the size of a hen's egg, lying in the right base. July 11, 1916,



Fig. 134.—Normal pyelogram of the right kidney one year following the implantation of the ureter into the bladder.

excision of the tumor and implantation of the right ureter was done. Papillary epithelioma was diagnosed pathologically. A cystoscopic examination Oct. 27, 1917, one year and three and one-half months after operation showed no recurrence. The catheter passed easily up the right ureter and negative urine was collected. Phenolsulphonephthalein output showed 15 per cent in the right ureter, and 17.5 per cent in the bladder. The pyelogram showed the right kidney to be normal.

The general condition of the patient was good (Fig. 134).

**CASE 5 (185582).**—A woman, aged sixty years, was admitted to the clinic Feb. 13, 1917, and a diagnosis of carcinoma of the bladder was made. March 21, 1917, a suprapubic excision of one-third of the wall of the bladder was done. One inch of the right ureter was removed and the left ureter was implanted into the base of the bladder. It was not possible satisfactorily to reconstruct the bladder. The involved portion of the urethra was removed also. Jan. 22, 1918, ten months after the operation, there was no evidence of recurrence of the tumor. The left meatus could not be seen; the right was normal. A catheter was passed well up the right ureter. The phenolsulphonephthalein output showed 12 per cent in the right ureter, and a trace in the bladder

in fifteen minutes. The left kidney was found to be functionless, probably because of the tension on the ureter necessary for its implantation.

**CASE 6 (69825).**—A man, aged fifty-four years, was admitted to the clinic June 27, 1912. A carcinoma of the left base and wall of the bladder was found. July 6, 1912, suprapubic resection of one-third of the bladder with cauterization of the base, and implantation of the left ureter, were done. Cystoscopic examination March 8, 1913, showed no evidence of recurrence. The left meatus spurted urine normally. In answer to an inquiry in August, 1916, the patient stated that he was in good health and had no urinary inconvenience.

**CASE 7 (186610).**—A man, aged fifty-four years, was admitted to the clinic Feb. 23, 1917. March 9, 1917, a suprapubic resection of one-third of the left wall of the bladder and one-half inch of the left ureter, with implantation of the ureter, was done for carcinoma. Oct. 18, 1917, cystoscopic examination showed no recurrence. The left meatus was widely open and spurted urine normally. A catheter passed easily and the specimen of urine showed a few pus-cells. Intravenous phenolsulphonephthalein appeared in four minutes, from the left ureter 4 per cent, and from the bladder 20 per cent. The catheter drained poorly. The pyelogram showed a normal kidney and ureter (Fig. 135). The patient's health is good.



Fig. 135.—Normal pyelogram of the left kidney seven months following the implantation of the ureter into the bladder.

**CASE 8 (213632).**—A man, aged forty-eight years, was admitted to the clinic Nov. 20, 1917. A suprapubic excision with cauterization was done at the base of the left wall of the bladder and base of the left ureter for multiple papilloma. One large growth the size of an orange was situated at the left meatus. Cystoscopic examination four months and twenty-two days after the operation showed no evidence of recurrence. The left meatus, which was located high up on the left wall of the bladder, was catheterized easily. Indigocarmine, dark blue in color, appeared in five minutes on both sides. The pyelo-ureterogram showed a normal pelvis and ureter throughout. Examination of urine from the left kidney was negative (Fig. 136). The patient has gained 8 pounds in weight and has no urinary inconvenience.

vaginal fistula following operation for cancer of the uterus five months previously. An implantation of the left ureter was done April 7, 1916. Eighteen days later a ureteral catheter was passed easily, and cloudy urine, showing numerous pus-cells, flowed rapidly for twenty minutes. Two ounces of urine were withdrawn; the specific gravity was 1.010. Before implantation could be accomplished the lower end of the ureter had to be dissected out of dense scar tissue.

CASE 15 (144658).—A woman, aged forty-two years, was admitted to the clinic Oct. 30, 1915. The patient had developed a right ureteral vaginal fistula following hysterectomy done at the clinic March 15, 1916, the right ureter was dissected free from the scar tissue and implanted into the bladder. A cystoscopic examination twenty days after the operation showed the end of the right ureter protruding into the bladder. It was not possible to catheterize on account of the obstruction. The left kidney was catheterized, and the differential functional

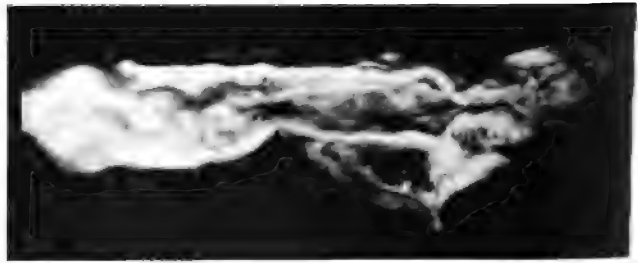


Fig. 138.—Partial stenosis at the lower end of the ureter with marked dilatation above. Specimen was obtained at necropsy four days following the implantation of the ureter into the bladder.

test showed 13 per cent in the left ureter and 2 per cent in the bladder in thirty minutes.

CASE 16 (163923).—A woman, aged twenty-one years, was admitted to the clinic June 27, 1916. The patient had suffered from incontinence since childhood. The right ureter was found opening into the urethra. Implantation of a widely dilated right ureter was done April 25, 1917. The cystoscopic examination four months later showed an infected hydronephrosis containing more than two ounces of cloudy urine. The phenolsulphonaphthalein output showed 15 per cent in the right ureter and 30 per cent in the bladder in fifteen minutes.

CASE 17 (215976).—A man, aged thirty-two years, was admitted to the clinic Dec. 7, 1917. An operation for diverticulum of the bladder was done Feb. 26, 1918. The left ureter was found opening into this pouch and was transplanted. On cystoscopic examination six weeks later it was impossible to get a satisfactory view of the transplanted

us. A No. 6 catheter was passed into the right ureter and a differential functional test done which showed 25 per cent from the right kidney and 12 per cent from the bladder.

**CASE 18 (210877).**—A man, aged fifty-four years, was admitted to clinic Oct. 15, 1917. Nov. 16, 1917, a suprapubic resection of one-half of the bladder, with implantation of the left ureter, was done for cancer. The patient died in the hospital on the fourth day after the operation. Necropsy showed advanced myocardial changes and pulmonary edema. There were multiple small cortical abscesses in the left



Fig. 139.—Necropsy on the twelfth day following the implantation of the right ureter into the bladder showed no obstruction at the site of anastomosis. The ureter and pelvis of the right kidney were slightly dilated. Both kidneys showed arteriosclerosis.

kidney and a slight hydronephrosis. The ureter was contracted at the site of the anastomosis and was dilated above this point (Fig. 138).

**CASE 19 (218877).**—A man, aged sixty years, was admitted to the clinic Jan. 12, 1918. Jan. 19, 1918, a suprapubic resection of the bladder and one and one-half inches of the right ureter, with re-implantation, into the dome of the remaining portion of the bladder, was done for extensive cancer. A small catheter was passed into the implanted ureter and brought out through the suprapubic wound. The patient died on the twelfth day from bilateral pulmonary emboli. There was no obstruc-

tion at the site of implantation. Both kidneys showed arteriosclerotic changes with slight dilatation of the right kidney pelvis (Fig. 139).

**CASE 20 (101710).**—A man, aged forty-five years, was admitted to the clinic March 11, 1914. A part of the right wall and base of the bladder was excised Dec. 14, 1917, with implantation of the right ureter into the base, for early epithelioma of the bladder. A small catheter was passed into the implanted ureter. The convalescence was uneventful for one month, when abdominal distention and coma developed and the patient died. Necropsy showed a general peritonitis with firm union



**Fig. 140.**—Necropsy one month after the implantation of the right ureter into the bladder showed no evidence of obstruction in either the ureter or the kidney.

of the implanted ureter and an old perivesical hematoma near the site of implantation (Fig. 140).

**CASE 21 (219087).**—A man, aged forty years, was admitted to the clinic Jan. 14, 1918. Jan. 22, 1918, a resection of the base and the right one-half of the bladder, with transplantation of the right ureter into the dome, was done for extensive cancer. The ureter was dilated to the size of a finger. A catheter was passed into the ureter. The cancer had extended into the perivesical fat. The patient died two months after the operation. Necropsy showed a large bilateral psoas abscess, extensive metastasis to the liver, and carcinomatous extension into the

perivesical area, with marked sloughing of tissues. The site of anastomosis could not be made out on account of the necrosis of the bladder



Fig. 141.—Necropsy two months after the implantation of the right ureter into the bladder. The site of implantation could not be definitely made out because of the sloughing of the remnant of the bladder. There was marked dilatation of both the ureter and the pelvis, and advanced pyelonephritis on both sides.

and the surrounding infiltration. There was marked bilateral dilatation of the ureters and kidneys (Fig. 141).

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## PROSTATIC CALCULI\*

E. S. JUDD AND J. L. CRENSHAW

A review of the records of the Mayo Clinic shows that from January, 1910, to July, 1918, 3180 patients were examined in whom symptoms were being produced by a pathologic lesion in the prostate gland. Of this number, 1825, or considerably more than one-half, were not operated on, and in the remaining 1355 a partial or complete prostatectomy was performed. Of the non-operated cases, some were inoperable because of too extensive malignancy while in others there were contra-indications to operation because of other complications and general conditions. A considerable number of the patients still come for treatment when the prostate has ceased to be the important consideration, and at a time when the relief of the urinary symptoms would be of no avail. Eleven hundred and seventy-one of the operations were prostatectomies performed for urinary obstruction caused by benign hypertrophy; 118 were for carcinoma, and 14 were for tuberculosis. Included in this group of 1171 cases are all of those in which a true hypertrophy existed and also those in which there was a large or small degree of hypertrophy in conjunction with the prostatitis. In most of the cases of simple prostatitis the patients responded fairly well to conservative treatment, but if hypertrophy interfered with the emptying of the bladder, it was necessary to operate. At times prostatitis apparently occurs in a special form, in that, as a result of this type of inflammation, stones are formed and deposited in the substance of the gland. It is to this type of prostatitis and the formation of these calculi that we wish to call attention, and also to contrast the condition with one in which stones that are not true prostatic stones become lodged in the prostatic region. In this same period, eight and one-half years, we have seen and treated or advised treatment in 20 cases of prostatitis in which true prostatic calculi were present, and also 11 cases in which it was necessary to

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operate for the removal of false prostatic stone. In most instances the false stones were removed by intra-urethral methods.

The occurrence of prostatic calculi is rare as compared with the occurrence of calculi in other parts of the urinary system. Because of the fact that in a considerable percentage of cases the symptoms are not directly owing to the stone, and the calculi is not suspected, in many instances the condition is overlooked.

The literature on this subject is made up largely of reports of single cases, although within the last year Kretschmer has collected in all, including his own, 173 cases. Some specialists consider the condition so rare as to be of no clinical importance, while others maintain that because of its rarity it is infrequently recognized, which is inexcusable since the condition, if diagnosed, can be completely remedied by proper measures.

Cases of prostatic calculi may be divided into three distinct groups. In two of these groups of cases are true prostatic stones as they are formed immediately within the substance of the gland; in the third group the stones are formed elsewhere,—usually in the kidney, sometimes in the bladder, possibly in a diverticulum of the urethra, and from there are passed into the prostatic urethra. These are known as false prostatic stones.

In Group 1 are placed the cases of true prostatic calculi in which the stones are the result of peculiar forms of prostatitis. There may be one or a number of stones formed at the same time. They evidently arise from the acini or ducts of the gland, and while they are usually small, they may attain considerable size. These calculi have the concretion and sediment of the prostate gland as a nucleus, and this is usually covered by layers of phosphates. There may be some urates as well in the formation, but the nucleus is considered the distinguishing feature. Examination of the nucleus for prostatic material will definitely determine whether or not the stones were formed within the prostate gland. Regarding the formation of such stones, Lund says that hard microscopic bodies called corpora amylacea form in the prostate at any age. They consist of sediment from the prostatic secretion, and at times become the nucleus for stone formation. Mineral salts, chiefly phosphate of lime, the triple phosphates, and bicarbonate of lime, make up the outer coat. The presence of stones in the gland, and also the presence of inflammation in the gland, cause considerable absorption and destruction of gland tissue so that it is usually but a honey-combed

formation, with calculi projecting from the different compartments. Often there are also multiple abscesses. Unquestionably, the prostate is the important feature, and stone formation is probably secondary. While the stones are generally distributed throughout the gland, they may occur in isolated pockets outside the gland proper, and some cases are reported in which the stones were located in pockets in front of the rectum, and were removed by incision into the wall of the rectum.

The symptoms are those of a severe prostatitis, and often the patient is treated for the inflammation, unaware of the fact that stones exist. If the stones project into the urethra, there will usually be urinary obstruction. In some instances stones have passed through the urethra and sometimes there is a history of hematuria, although these features are not at all diagnostic. One case is mentioned by Thomas in which the patient passed 101 stones. Pain is prevalent and usually of the same character as that of ordinary prostatitis, except that it is apt to be more severe. There is much tenderness throughout the perineum and especially on rectal palpation of the prostate, even when stones cannot be felt. The diagnostic characteristics lie in the character of the gland on rectal palpation and in the shadows shown in x-ray examinations of this region. Frequently the condition can be definitely diagnosed by palpation, as the stones may be felt and there is a sense of crepitation on pressure. If the stones are well buried in the gland substance or are lying in the prostatic urethra, they may not be felt. Practically all such stones will cast shadows on x-ray examination, and the diagnosis is very accurate by this method. It is important that an x-ray examination should be made in all cases of protracted or uncertain prostatitis.

In Group 2 are classified those cases in which the calculi, in all probability, have their origin in the acini and ducts, the same as in Group 1, but instead of being associated with an inflammation in the gland, there is an associated hypertrophy. In these cases the hypertrophy is probably the essential pathology and is the cause of all or nearly all of the symptoms. Often there is nothing to direct attention to the stones until the hypertrophied process is enucleated from the gland. The stones usually occur in the form of sand, and while this may be generally distributed through the hypertrophied tissue, more often most of it seems to be between the hypertrophy and the capsule. Such stones rarely attain to any considerable size, and in all probability are not in themselves responsible for symptoms, although they should be taken into

consideration when present with the hypertrophy. They are usually numerous and have the same formation as the larger stones. Sometimes this sandy material may be felt on rectal examination, and sometimes the small stony particles are grouped together so that they cast a shadow on x-ray examination.

Special mention should be made of the differential diagnosis between prostatitis, hypertrophy with stone formation, and carcinoma of the prostate, which is at times quite difficult in that the hard, nodular prostatic carcinoma presents much the same sense of feeling as the stones. In such cases the cystoscopic examination may be very helpful in settling the diagnosis, as in the event of prostatitis it reveals the dilated prostatic ducts and often the stones will be seen projecting from them. Tuberculosis of the prostate may, at times, simulate prostatitis with stones, but more often the differentiation is not difficult. An x-ray examination may be necessary in such cases and it is essential that the exposure should be made low enough to take in the symphysis pubis.

In Group 3 are the cases of false prostatic calculi in which the stone is always found in the prostate, usually in the prostatic urethra, but is not a true prostatic stone. While it is not always possible clinically to distinguish this condition, nevertheless the early history is frequently suggestive. The stones usually originate in the kidney, bladder, or diverticula of the urethra, and in many instances there is a history of former renal colic during the time the stone passed, or if the stone has been in the bladder, the symptoms produced by the irritation there will suggest the presence of a stone. The stones pass from the bladder into the prostatic urethra and become lodged there. The symptoms at that time are great pain and urinary obstruction. The stone can usually be felt by sound or cystoscope. Whether the stone is a true prostatic calculus or a false one often cannot be determined until it is removed and examined. The stone which forms in the kidney is largely a urate formation, and can readily be distinguished from a prostatic calculus. The x-ray will disclose the presence and location of these false prostatic stones, which may become very firmly lodged in the tissues of the prostatic urethra and require considerable effort to remove them. In many instances it will be necessary to accomplish this by an open operation, and great care must be exercised to preserve the bladder sphincter. In several instances in our series it has been difficult to remove these stones without producing considerable trauma to the surrounding tissues, but in a number of instances we were able to remove

the stones lodged in the urethra very easily with urethral instruments and, of course, this should always be tried first.

The treatment of all types of prostatic calculi is to remove the stone and remedy the accompanying condition. In cases of true prostatic calculi in which there is usually a severe prostatitis I believe that treatment should be radical. In some instances the condition can be relieved by massage and irrigation, the stones being forced into the urethra and washed out. However, continuing this treatment over any length of time is not justifiable, and if the stones are not easily removed, an operation is indicated. Some surgeons have advised, as an operative procedure in these cases, a perineal prostatotomy, and the scraping out of the stones and draining the infected prostate. This method of procedure may be satisfactory in some cases, but under ordinary circumstances it is much better to do a transvesical operation. In this manner we are more certain to preserve the bladder sphincters intact; moreover, the prostate may be so extensively infected that the greater part of it should be removed to insure a complete cure and to prevent return of symptoms. In many instances the prostate is so completely destroyed as to have lost all its function; it is of no service, and may make trouble in the future. If the inflammation is not extensive, stones may be removed easier and with less danger of other difficulties by transvesical operation than through a perineal incision. It is not necessary to operate especially to remove the sandy material, which is always found in conjunction with some hypertrophy of the gland, but when this condition complicates a hypertrophy, it is well to be careful to remove all the sandy material from the prostatic capsule. This can be done easily after the enlargement has been enucleated. In cases in which false prostatic calculi pass down the urethra and can be removed by the cystoscope or other urethral instruments, this should be done, but if the calculi are firmly wedged into the urethra, it will be best to remove them by transvesical operation.

Prostatic calculi are in reality complications arising in cases of prostatitis, hypertrophy of the prostate, and kidney and bladder stone. While they are rare, they are common enough, all cases considered, to command attention. By bearing in mind that calculi may complicate any one of these conditions, that with the present methods of examination they may be recognized, and furthermore that the treatment of the condition is generally entirely satisfactory, we should be able to add a great deal to the relief of patients suffering from prostatic calculi.

# TECHNIC OF CLINICAL DATA ON THE 20 CASES OF TRUE PROSTATIC STONES

*Patients.*—Twelve operated on, 8 not operated on. Youngest, thirty-four years; oldest, seventy-six years; average, fifty-seven years.

*Symptoms.*—Four weeks shortest duration; thirty-seven years longest duration; fifteen years average duration; 2 had no symptoms.

*X-ray.*—Positive in 15; negative in 1; questionable in 1, and not made in 3.

*Stones.*—Palpable per rectum in 16; crepitation per rectum in 6.

*Number of stones.*—One in one case; 3 in one case; many in 18 cases.

*Size and location of stones.*—One case a solitary stone, 2 by 3 cm., in the substance of the gland; 4 cases, a medium size stone in the substance of the gland; 9 cases, many small stones in the substance of the gland; 1 case, one large and many small stones in the substance of the gland; 1 case, many small stones in a pocket of the left lobe; 2 cases, sand; 2 cases no record.

*Condition of gland.*—Eight cases, adenofibromatous hypertrophy; 8 cases, chronic prostatitis; 2 cases, hypertrophy and chronic prostatitis; 1 case, acute prostatitis; 1 case, normal.

*Previous Neisserian infection.*—Eight cases test positive; 10 cases denied; 2 cases not recorded.

*Previous operations or diseases other than Neisserian infection influencing the condition.*—Two cases, periurethral abscess (cause unknown, 1; trauma, 1); 2 cases, history of renal colic, stone in the prostate but not in the kidney; 5 cases, stricture (Neisserian infection, 4; trauma, 1; urethrotomy 2, sound 2); 1 case, renal stones (nephrectomy); 1 case prostatic stone (prostatotomy); right castration (cause unknown); 1 case, Raynaud's disease; 8 cases, no operation.

*Genito-urinary complications (other than prostatic).*—Eight cases none; 2 cases bladder stone; 1 case bladder stone and diverticulum of bladder; 1 case perineal abscess and fistula and stone in the right kidney—infection of the left kidney; 2 cases traumatic stricture and fistula; 5 cases stricture; 1 case prostatic abscess and postoperative sinuses.

*Urinalysis.*—Nineteen cases, acid; 1 case, alkaline; 9 cases, red blood count; 19 cases, pus; 1 case, negative.

*Symptoms.*—Thirteen cases, pain; 13 cases, frequency; 13 cases, difficulty; 4 cases, hematuria; 3 cases, stones passed (1 case 26 stones; 1 case 6 stones); 2 cases epididymitis; 4 cases, incontinence; 9 cases, residual (not tested 7); 2 cases, no symptoms. In some cases urgency and burning.

*Operation.*—One case, perineal prostatotomy; 1 case, suprapubic prostatotomy; 8 cases, suprapubic prostatectomy (complete); 2 cases, suprapubic prostatectomy (partial).

# THE CLINICAL DATA IN 11 CASES OF FALSE PROSTATIC STONES IN WHICH OPERATION WAS DONE

*Cases.*—Eleven: Youngest, sixteen years; oldest, seventy years average, forty-four years.

*Duration of symptoms.*—Five months shortest duration; eighteen years longest duration; seven years average duration.

*X-ray.*—Positive in 6; negative in 1; not made in 4.

*Stones.*—Palpable per rectum in 6; indeterminate in 1; not recorded in 4; crepitation per rectum in none.

*Number of stones.*—Solitary stone in 9 cases; multiple in 2.

*Size and location of stones.*—One case, one stone in prostatic urethra; 1 case, multiple perineal fistulas and stone in prostatic urethra above stricture; 1 case, one phosphatic stone, medium size, in a pocket in posterior urethra; 1 case, one large sharp stone, mucous membrane not lacerated, prostate flattened out by stone; 1 case, one kidney stone wedged in prostatic urethra after fulguration of left meatus for its removal, removal through cystoscope; 1 case, one large irregular stone in prostatic urethra; 1 case, one stone one-half inch in diameter, rough, irregular, impacted in sacculated urethra; 1 case, many phosphatic stones and necrosis; prostatic urethra packed with stony material; 1 case, dilated prostate full of stones, impermeable stricture; 1 case, one large irregular stone, urethra dilated to size of bladder; 1 case, one large, irregular, pear-shaped stone, large dilatation of urethra above stricture.

*Previous Neisserian infection.*—Four cases test positive; 3 cases denied; 4 cases not recorded.

*Previous operations or diseases other than Neisserian infection, influencing the condition.*—One case, perineal prostatectomy; 1 case, suprapubic prostatectomy; 1 case, perineal exploration; 1 case, stricture of urethra; 1 case, stricture and bladder stones (operation); 1 case, large bladder stone (operation); 1 case, cystitis; 1 case, ruptured bladder; 1 case, ruptured urethra; 1 case, left kidney colic and later bladder irritation; 1 case, negative.

*Genito-urinary complications.*—Three cases, negative; 1 case, multiple bladder stones; 1 case, contracted bladder; 1 case, branched stone and pyonephrosis of left kidney; 1 case, cystitis and pyelonephritis; 1 case, necrotic fistula, fractured pelvis, bladder stones, and pelvic abscess; 1 case, perineal fistula and stricture; 1 case, anterior stricture; 1 case, stricture and left kidney stone.

*Urinalysis.*—Six cases, acid, 4 cases, alkaline, 1 case not reported; 7 cases, red blood count; 10 cases, pus; 1 case, not reported.

*Symptoms.*—Eleven cases, pain; 11 cases frequency; 11 cases difficulty; 5 cases, hematuria; 5 cases, passing stones; 2 cases, incontinence; 1 case, residual; 3 cases, not tested.

*Operation.*—Five cases, suprapubic cystostomy; 3 cases, perineal lithotomy; 1 case, suprapubic cystostomy and urethral dilatation; 2 cases, stones removed through cystoscope.

*Probable origin of stone from history and pathology.*—Six cases, bladder stones; 2 cases, bladder; 3 cases, left kidney.

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## DIVERTICULA OF THE BLADDER\*

E. S. JUDD

The increasing frequency with which we have encountered diverticula of the bladder in the past few years has led me to review the cases that have been treated at the Mayo Clinic. Presumably this condition does not occur more frequently now than formerly; though with a somewhat better understanding of the surgery of the bladder in general, and with the great advance in methods of examining all patients with bladder trouble, many more are being presented for surgical treatment.



Fig. 142.—(179245.) Cystogram of a diverticulum from the left base of the bladder, opening 2 cm. posteriorly and to the left of the left meatus. Resection of the diverticulum.

### ETIOLOGY AND PATHOLOGY

The question as to whether or not these diverticula, as well as those occurring in other parts of the body, are congenital or acquired, has been widely discussed, and many convincing articles have been published supporting each contention. Undoubtedly diverticula of the bladder may be congenital, as instances have been reported in infants and

small children, and it would certainly seem that in most of such cases there must have been some congenital defect in the bladder as a primary etiologic factor. If the condition were always due to obstruction, it would probably occur more often in cases in which the stream of urine is obstructed. It has been suggested that the weak points in the wall

\* Read before the American Surgical Association, June, 1918. Reprinted from *Ann. Surg.*, 1918, lxxiii, 298-305.

of the bladder may be at the site of one of the embryonic buds. While it seems possible that a diverticulum might occur at one of these points, and that this embryonic weakening might be the factor in certain cases, on the other hand, my observation leads me to believe that the point of dereliction is not constant enough to indicate that the majority originate from these buds. In most of our cases the opening of the diverticulum was not far from one of the ureteral meatuses, but the relationship to the meatus was not at all constant, so that, in some cases, the

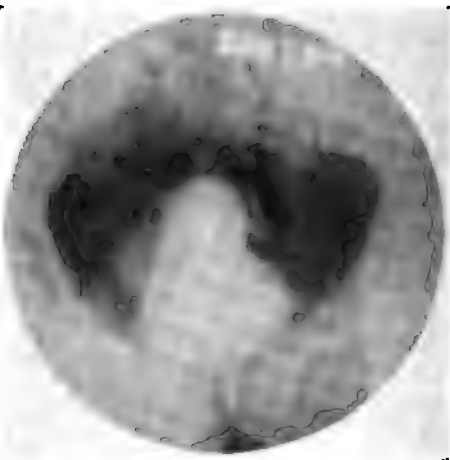


Fig. 143.—(206754.) Cystogram of a diverticulum from the right base of the bladder, opening 2 cm. from the right meatus. Resection of the diverticulum.

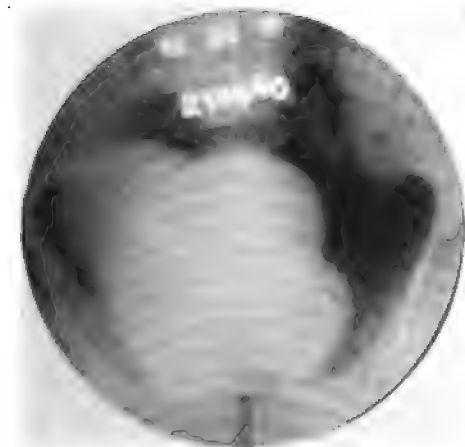


Fig. 144 —(214640.) Cystogram of a diverticulum of the right wall of the bladder, opening about 3 cm. posteriorly and to the right of the right meatus. Resection of the diverticulum.

diverticulum opened into the bladder in front of the meatus of the ureter, in others, well above it or posterior to it, and in some cases in the base of the bladder posterior to the trigone. It is certain, however, that the greater number of the diverticula do have a proximity to the ureter. The diverticulum that occurs in the dome is rarely seen and, apparently, is an entirely different type than the diverticulum under discussion.

The close relationship of the diverticulum to the ureter may mean that the diverticulum, especially if it is of considerable size, will inter-

fere with the ureter. Several cases have been reported in which a hydro-nephrosis and a pyonephrosis have developed, apparently due to this

interference with and pressure on the ureter. Cabot reports an inter-



Fig. 145.—(206754.) Stylet coiled in the diverticulum from the right base of the bladder. Opening 2 cm. from the right meatus. Resection of the diverticulum.

esting case in which bilateral diverticula were interfering with both ureters. In a series an instance of this kind has not been observed, though in several instances we have been able to demonstrate that the ureteral meatus was just at the border of the opening of the diverticulum, and that in reality the ureter *did* open into the diverticulum. In one case the ureter emptied into the sac of the diverticulum, and it was necessary to divide the ureter and reimplant it into the new opening in the bladder. In several other cases in which the ureteral opening was marginal the adjoining mucous membrane was turned into the bladder closure, the meatus being preserved. It seems advisable to employ this method whenever it can be done. While a marked trabeculation of the bladder is often seen in cases of diverticula, at the same time it is not at all likely that the trabeculae will ever become diverticula. Diverticula are true pouches, and in a bladder in which they exist there is always residual urine and other evidence of an incapable bladder. It is because of this that the trabeculae form, just as they often do in cases in which the inability to empty the bladder is due to the obstructing prostate. When the difficulty is overcome by removing the diverticula.



Fig. 146.—(155042.) Stylet coiled in the diverticulum of the right base of the bladder. Opening 3 cm. from the right meatus. Resection of the diverticulum.

trabeculae disappear, as in prostate cases when obstruction is relieved (Figs. 142-147).

#### CLASSIFICATION OF DIVERTICULA

Diverticula have been classified as congenital and acquired. The congenital type is formerly thought to be those in which all coats of the wall of the bladder were involved in the diverticulum; the acquired type had a sac composed of mucous membrane only (Figs. 148-155). This classification, made by Engsch some time ago, would not, I think, hold according to most observers at the present time.

It seems to be the consensus of opinion that a congenital deformity, or lack of development, is a factor in all these cases. However, there seem



Fig. 147.—(224370.) Stylet coiled in the diverticulum from the left base of the bladder. Opening 2 cm. posterior and to the left of the left meatus. Resection of the diverticulum and prostatectomy.



Fig. 148.—(226631.) Diverticulum.

to be two distinct types—one in which the diverticulum is associated with an enlargement of the prostate, and which has led some observers to believe that it is the result of the obstruction from the prostate, the other occurring in much younger men, in which there is no evidence

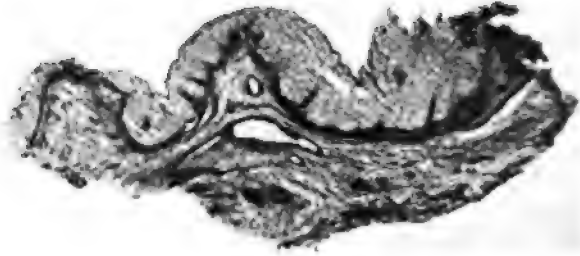


Fig. 149.—Same as Fig. 148. Low power section through the entire thickness of a large diverticulum, showing the mucous membrane.

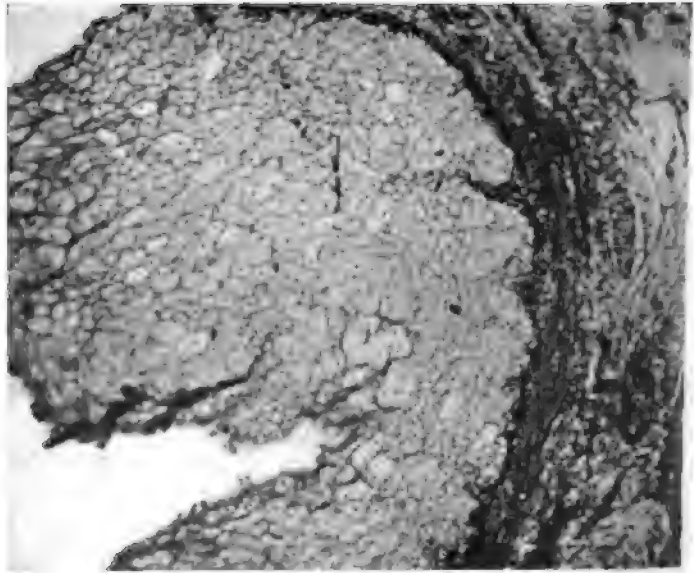


Fig. 150.—Same as Figs. 148 and 149. High power showing mucous membrane and strand of smooth muscle of a large diverticulum.

obstruction from any cause. The latter patients will frequently have more residual urine than those with an enlarged prostate and a diverticulum. In either of the two types the diverticula may be multiple, though usually there is a large sac and one or more small ones.

Many cases have been cited to show that obstruction is not a factor in the causation of the condition. It has been demonstrated repeatedly that in case there is an obstructing enlargement in the prostate associated with diverticulum of the bladder, that the removal of the obstruction will not relieve the situation; and, furthermore, that the removal of the prostate and diverticulum will completely relieve all symptoms. I wish to emphasize this point particularly because I believe that many of the patients with prostatic trouble, who continue to have the so-called cystitis and residual urine after the obstruction has been removed, are

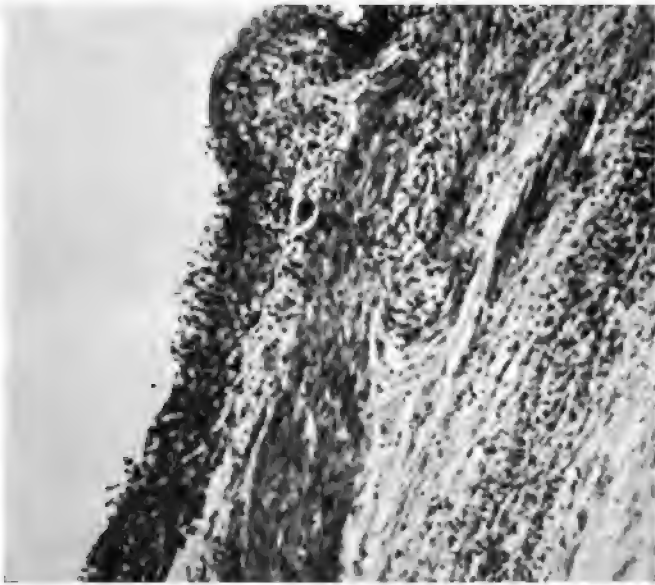


Fig. 151.—Same as Figs. 148, 149, and 150. Different area from Fig. 150. Showing scanty mucous membrane and strands of smooth muscle.

in reality suffering from diverticula, and that if a careful examination is made for a diverticulum at the time of the prostatectomy in such cases this error will be avoided. I feel certain that we have overlooked a number of diverticula in examining prostatic patients, and that many are now receiving irrigations of the bladder, and catheterizations under the assumption that the symptoms are produced by cystitis, when in reality they are caused by the diverticula.

Whether the sac is composed of all the coats of the bladder, or whether it is composed of the mucous membrane alone, does not seem

to draw a line between the etiology of the congenital and acquired types in these cases. There must be some congenital defect which allow these sacs to develop, though their development may be ad-



Fig. 152.—(49150.) Diverticulum



Fig. 153.—Same as Fig. 152. Low power showing smooth muscle in fat. The mucous membrane is absent.

and increased by an obstruction to the urinary outflow. In the young man with this condition the bladder is usually large, but the wall is not particularly thick, and may appear quite normal. In the type occur-

in older men, especially with prostatic trouble, the wall of the bladder is very thick from hypertrophy. In such cases the sac is adherent and firmly attached to the side of, or beneath, the thick bladder, and is frequently is much inflamed by cystitis and evidence of old and recent infection, without perforation. Infection usually exists in the cases in which the sac lies between the bladder and the rectum. In young men the sac is thin, and is not firmly attached in the surrounding tissues, so that it is readily separated with very little dissection. Stagnation in the dependent sac favors infection, which results



Fig. 154.—(206754.) Diverticulum.

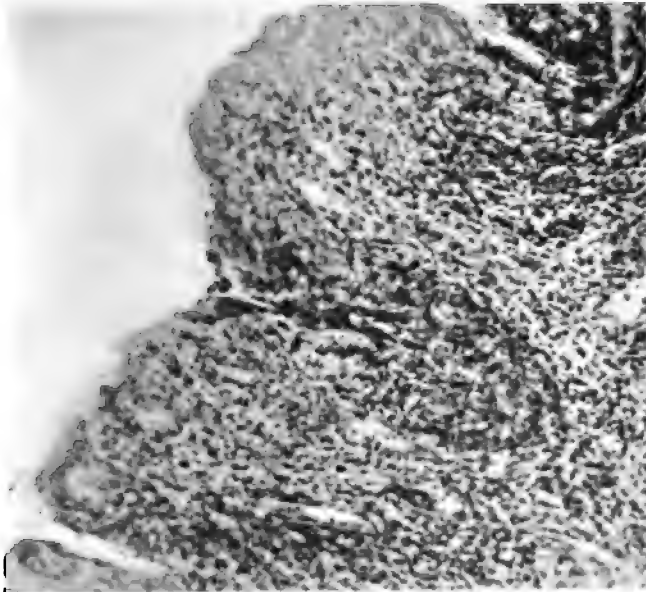


Fig. 155.—Same as Fig. 154. High power showing diverticulum. Mucous membrane with absence of muscle.

in diverticulitis and consequent cystitis. It has been our experience that, in the infected case, apparently the greatest degree of infection is in the



sac, though there is all the evidence of infection in the bladder as well is not unusual, in dilating the orifice of the diverticulum, to see thick escaping into the bladder, giving the appearance of opening an abscess under tension. Pericystitis and diverticulitis are always present to some degree in the case of the thick-walled sac. Calculi are often found in the sac, as was the case in four of our patients. In one of our cases previously reported by Martin, a dumb-bell shaped stone, partly in the bladder and partly in the sac, was found. There was carcinoma in the sac in one of our cases, and carcinoma and stone in another.

### CLINICAL FEATURES

Diverticulum of the bladder occurs almost exclusively in the male. In very few cases have been reported in the female. The characteristic feature of the clinical syndrome is a feeling that the bladder is not emptying. This comes on almost immediately after voiding, with the inability to repeat the act of voiding and the second time to pass a considerable amount of urine. Urination may be painful, particularly if the diverticulum is large. The sac may be palpated in some cases, especially through the rectum. Frequency and burning with difficulty of urination were present in most of our cases. Such symptoms always occur in cases after infection has taken place. Patients with diverticula have all the features of marked cystitis, and often are treated over long periods for this condition. It is almost a pathognomonic sign of diverticulum to have a considerable amount of urine, thick with pus, escape from the catheter just at the time the bladder was supposed to be entirely clean. The urine in these cases is very foul, and on opening the bladder to perform a prostatectomy or drainage operation, should this foul urine be detected, a diverticulum should be suspected and looked for. In the long-standing case evidence of a kidney infection, and insufficient renal function, becomes marked. A low percentage of phenolsulphonephthalein return is not a definite contraindication to surgical treatment in all of these cases; many of the patients do well in spite of this condition.

### DIAGNOSIS

While the diagnosis is suggested by the clinical features, the accurate determination of the condition rests with the cystoscopic examination, and the employment of the leaded catheter and x-ray, or by the making of a cystogram, which is of great value in any doubtful case. The cysto-

scope will usually reveal the condition, though in the case of an enlarged prostate, or in very marked cystitis, when the mucosa of the bladder is greatly congested and distorted, it may be impossible to see the opening through the cystoscope, and a cystogram should then be made. In other instances the opening of the diverticulum into the bladder is very small and difficult to see, but the colloidal silver solution will readily pass into it and the diverticulum can be seen when the röntgenogram is made. In any very marked case of cystitis in which the bladder is

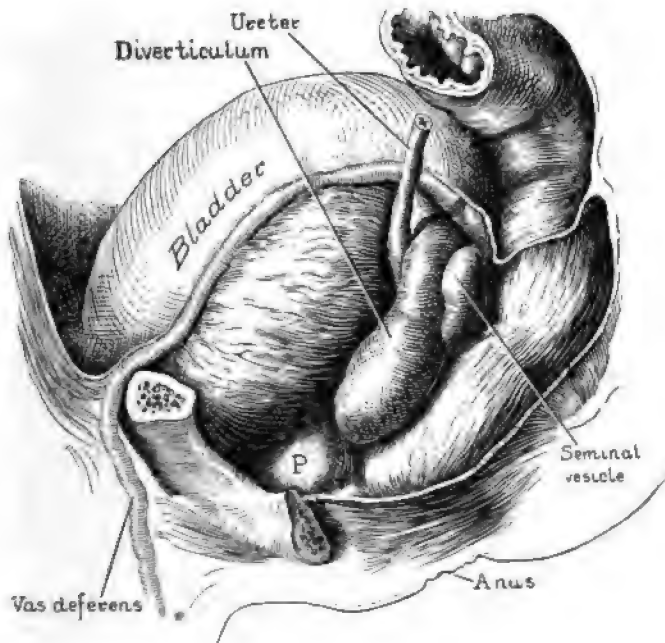


Fig. 156.—Diagrammatic sketch, showing the relation of the diverticulum to the bladder, prostate, rectum, seminal vesicle, and ureter.

to be drained a diverticulum should be searched for, even if these methods of examination fail to show one, as it is possible that the opening might be closed and the diverticulum not recognized at the time of the examination. In view of the fact that I have had a great deal of difficulty in making a diagnosis in some of these cases, particularly in those in which there was an obstructing enlargement of the prostate, it seems well to emphasize the necessity of a careful exploration of the bladder at the time of performing the prostatectomy in cases showing marked cystitis and infection at the time of the examination. A diverticulum

should be suspected in the patient who has had a **prostatectomy** and still has a considerable amount of residual urine, particularly if there is much evidence of infection which does not respond to the ordinary treatment.

The present report is based on a group of 44 patients operated between February, 1908, and March, 1918. All the patients were males, varying in age from eighteen to seventy-three years. Twelve gave a history of gonorrheal infection, and 3 of the 12 had been treated for stricture of the urethra. There is no evidence to show that the

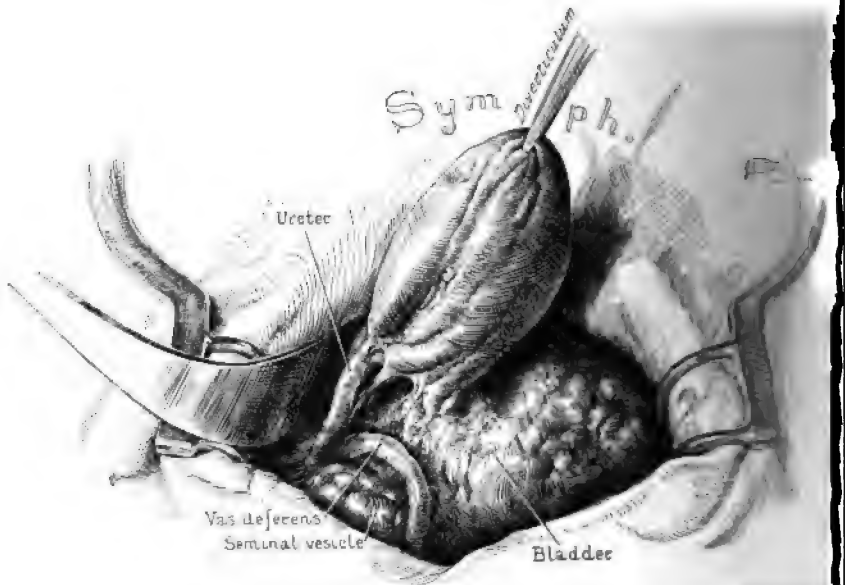


Fig. 157.—(215976.) Relation of the neck of the diverticulum to the ureter and vas deferens after the sac of the diverticulum has been dissected out from beneath the bladder.

infections or strictures were in any way responsible for or had anything whatever to do with the formation of the diverticula. Six of the 44 patients had been operated on previously for these symptoms without relief. Eight of the patients gave a history of some form of trauma, which might have been a factor to consider in the etiology, but the association was too remote to prove that the trauma had anything to do with the weakening of the wall of the bladder, or that it in any way had been a cause of the diverticula. We believe the trauma was merely incidental. Seventeen of the patients also had an enlargement of the prostate, and the remaining 31 had cystitis, graded at least three on a

of 4. There was stone in the bladder in 6 of the patients, and noma in 4; in one the carcinoma originated within the diverticulum.

At operation the opening of the diverticulum was found in the of the bladder, or on one or the other of the lateral walls not far the ureteral opening in 39 of the 44 patients, which shows that a percentage of such diverticula originate in one of these regions.



Fig. 158.—(215976.) The situation of the diverticular sac on the left posterolateral wall and at the base of the bladder. The ureter enters the sac instead of the bladder. The cavity of the sac is approximately half the size of the bladder cavity.

The greatest number, 19, were found near the base of the bladder on the right wall. Bladder trabeculation, 3 on a scale of 4, was noted in 18 of the 44 patients.

### TREATMENT

In reviewing the literature, and from our own records, it stands out clearly that palliative treatment and any other form of treatment other

than excision of the diverticular sac has not given good results. Mortality as high as 83.1 per cent has been reported in cases in which there was a diverticulitis at the time of the operation. This percentage has been very greatly reduced. In the young man without infection the results are uniformly good, though complete recovery may be slow. In some of our cases the wound was slow in healing, and in others several ounces of residual urine persisted for a number of weeks, though eventually it almost entirely cleared up. Something can be accomplished

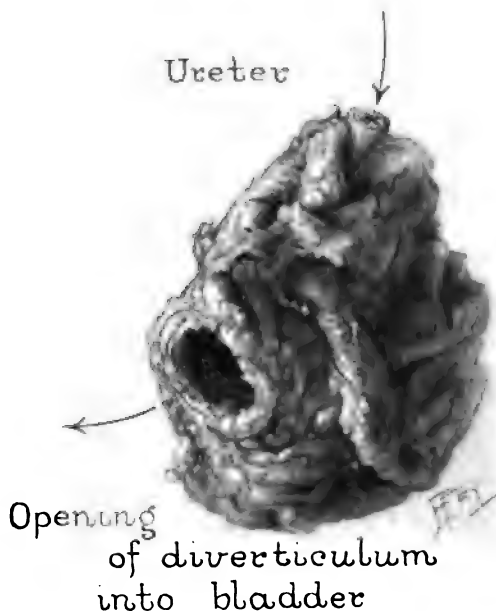


Fig. 159.—Diverticular sac and its opening, which communicates with the bladder. Note the ureter entering the sac.

by preliminary washings of the bladder and by employing methods to stimulate renal function in cases in which it seems necessary. Those who have had the most experience with these cases seem to be unanimous in the feeling that the proper treatment for any of these diverticula is complete excision of the sac, and that any treatment less radical will not be satisfactory. Our experience bears this out. Intravesical treatment, as can be readily seen, is of no avail except as a palliative when operation is contraindicated, or preliminary to operation. Drainage of the bladder, even as a preliminary step, will seldom help enough to

warrant its being done. We have drained a number of times in these cases, both at the time of the prostatectomy and when the diverticulum was the only lesion. I now believe that it is far better, under ordinary circumstances, to remove the diverticulum at the same time. Suprapubic drainage of the bladder, even when the drainage-tube extends into the diverticulum and is left there for a long time, will not help permanently. So far as I am aware, the less radical operations, such as enlarging the opening of the diverticulum and doing a plastic operation on the opening, and of anastomosing the diverticulum to the bladder, are not satisfactory. Therefore the treatment resolves itself into the excision of the diverticulum as soon as the patient's general and local condition has been improved as much as possible.

The operation consists in first making a fairly good-sized opening into the bladder through the prevesical space, and locating the opening of the diverticulum, after all the pus and infected mucus has been cleared away. The prevesical tissue should be protected against infection in every way possible. Ingenious methods have been devised for filling the diverticulum by means of

an air-filled rubber bag (Lerche) and for filling the sac with gauze (Lower) which is packed into the sac beforehand, to facilitate its removal. Such devices seem to help considerably. Whenever possible I prefer to pass one or two fingers into the diverticulum and then make the dissection through the prevesical tissues down on to the sac, which is also being lifted out by the fingers within it. This method is not new; it can be employed in almost all cases, and is especially helpful when the sac is firmly attached to the surrounding tissues. If the sac lies high up and is covered by peritoneum, it may

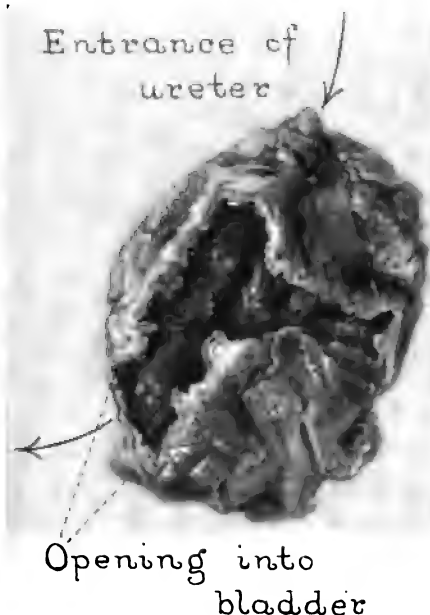


Fig. 160.—(215976.) The diverticulum after it has been cut in half. Note the communication opening into the bladder and the entrance of the ureter into the diverticulum.

be best to open the peritoneum, though, as a rule, this is not necessary. After the sac has been completely freed from the surrounding fatty tissue, the neck is severed, the opening in the bladder is closed, and a drain is placed in the prevesical space which the sac occupied. The suprapubic opening in the bladder is closed, with the exception of the place for the drainage tube. The difficulties of the operation lie in separating the sac from the surrounding tissue, particularly if the sac is



Fig. 161.—Finger passing through the incision in the dome of the bladder into the neck and cavity of diverticulum. The diverticulum being lifted out of the surrounding prevesical tissues.

thick-walled, and if there is a great deal of old infection and scar tissue. The vas deferens and the ureter, both of which will come into view in many of the dissections, should always be avoided (Figs. 156 and 157). Occasionally it will be necessary to divide the ureter and re-implant it in a new area in the bladder, as I did in one of our cases (Figs. 158–160, Case 215976). If there is an enlargement in the prostate, it should be removed at the same time (Figs. 161 and 162).

In this series of 44 patients, so far as we have been able to deter-

all but the  
a drainage  
age was  
been up  
had gone  
4 patients

	CASES
adder for cancer, prostatectomy, and resection of	1
diverticulum and transplantation of the ureter	1
prostatectomy	5
removal of stones	6
diverticulum and drainage of the bladder	4
adder and urethra	1

REPORTED IN THE 44 CASES, 10

	LENGTH OF LIFE	CAUSE OF DEATH
	2 days	Pyelonephritis
	4 days	Acute septic nephritis
prostatectomy	25 days	Bilateral pneumonia
diverticulum	28 days	Pulmonary embolus
diverticulum	1 month	Pyelonephritis
	2 months	Pyelonephritis
adder stone	2½ months	Pyelonephritis and peri-vesical abscesses
adder	9 months	Not known
diverticulum contain-	12 months	Not known
	36 months	Not known

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Enter-



**FORTY-FOUR PATIENTS OPERATED ON FROM FEBRUARY, 1908, TO MARCH, 1918. YOUNGEST, EIGHTEEN YEARS; OLDEST, SEVENTY-THREE YEARS; AVERAGE AGE, FIFTY-TWO YEARS**

History of venereal infection.....	
Urethral stricture in 3 (sound passed in 1, stricture cut in 2)	
Previous operation on the bladder (elsewhere).....	
Previous perineal prostatectomy (here).....	
Symptoms dating from previous trauma.....	
Enuresis since childhood.....	

**FIRST SYMPTOMS NOTED**

Hematuria.....	
Difficulty in urinating.....	
Frequency.....	

**SYMPTOMS**

Repeated urination.....	
Hematuria.....	
Pyuria.....	
Burning on urination.....	
Frequency.....	
Difficulty in urinating (catheter used in 9).....	
Loss of weight noted.....	
Average loss of weight, 15 pounds.	
Cystoscopic examination in.....	
Hypertrophied prostate.....	
Cystitis (average 3).....	
Bladder stone.....	
Stone and carcinoma.....	
Carcinoma (carcinoma in diverticulum in 1).....	
Cystoscopic localization of the diverticulum.....	
Dome of bladder.....	
Left wall and base.....	
Right wall and base.....	
Base.....	
Multiple diverticula of base.....	

**URINALYSIS**

Pyuria.....	
Hematuria and pyuria.....	
Location of the diverticulum at operation.....	
Right wall and base (10 near right ureter).....	
Left wall and base (6 near left ureter).....	
Left ureter in diverticulum.....	
Floor and base.....	
Dome.....	
Bladder trabeculation, average 3.....	
Bladder stones.....	
Carcinoma.....	
Carcinoma and stone.....	
Hypertrophy of the prostate.....	
Stones in the diverticulum.....	
Carcinoma in the diverticulum.....	
Carcinoma and stones in the diverticulum.....	

**TYPE OF OPERATION**

Intraperitoneal resection of the diverticulum.....	
Extraperitoneal resection of the diverticulum.....	
Extraperitoneal resection of the diverticulum and prostatectomy.....	
Extraperitoneal resection of the diverticulum, prostatectomy, and removal of stone.....	

## CASES

Extraperitoneal resection of the bladder for cancer, prostatectomy, and resection of the diverticulum . . . . .	1
Extraperitoneal resection of the diverticulum and transplantation of the ureter . . . . .	1
Drainage of the bladder and prostatectomy . . . . .	5
Drainage of the bladder and removal of stones . . . . .	6
Enlarging the opening of the diverticulum and drainage of the bladder . . . . .	4
Separation of septum between bladder and urethra . . . . .	1

## DEATHS REPORTED IN THE 44 CASES, 10

TYPE OF OPERATION	LENGTH OF LIFE	CAUSE OF DEATH
Drainage of bladder . . . . .	2 days	Pyelonephritis
Drainage of bladder . . . . .	4 days	Acute septic nephritis
Drainage of bladder and prostatectomy . . . . .	25 days	Bilateral pneumonia
Extraperitoneal resection of diverticulum . . . . .	28 days	Pulmonary embolus
Extraperitoneal resection of diverticulum . . . . .	1 month	Pyelonephritis
Drainage of the bladder . . . . .	2 months	Pyelonephritis
Drainage of bladder and removal of stone . . . . .	2½ months	Pyelonephritis and peri-vesical abscesses
(carcinoma in the diverticulum)		
Enlargement of opening in diverticulum . . . . .	9 months	Not known
Extraperitoneal resection of the diverticulum containing carcinoma . . . . .	12 months	Not known
Drainage of the bladder . . . . .	36 months	Not known

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## THE FREQUENCY OF ADENOMYOMA OF THE UTERUS\*

W. C. MACCARTY AND R. H. BLACKMAN

Since the publication, in 1903 and 1908, of the excellent and complete monographs on the subject of adenomyoma of the uterus by Dr Thomas S. Cullen but few articles have been contributed to the literature. In view of the fact that his report contained only 73 (5.7 per cent) adenomyomas in 1283 myomas of the uterus, and since these figures have not been confirmed by an equally large series, it seems timely to add a report from the Mayo Clinic.

Nothing in so far as gross and microscopic description or the origin of this condition can be added to what has already been so well presented.

Between 1906 and 1918 (October 1) 3388 fibromyomatous uteri were removed in the clinic. Two hundred and eleven (6.43 per cent) of these contained adenomyomas. In 5 cases the tumor was in the fallopian tubes. The frequency is somewhat greater in this series than in that of Cullen, but the figures are so close that from 5 to 7 per cent expresses it safely.

The last 109 cases of the series were studied with reference to certain clinical features which might be intimately associated with the condition. Ninety-five patients (86 per cent) were married; 41 per cent gave histories of having had miscarriages; 50 per cent suffered from profuse and prolonged uterine bleeding, and 31 per cent from irregular bleeding. The average age of puberty was 14.3 years. Sixty-five per cent of the married women had borne living children. In 5.5 per cent of the cases epithelioma of the cervix or carcinoma of the body of the uterus was associated, neither of which conditions bore any apparent relationship to the adenomyomas. In 72 per cent other pathologic pelvic conditions were associated, such as ovarian cysts, chronic or acute salpingitis, uterine or cervical polyps, cystic cervicitis or prolapsus uteri. In no case without the association of a malignant condition was the

\* Reprinted from Ann. Surg., 1919, lxix, 135-137.

clinical diagnosis one of malignancy. In no case was a positive clinical diagnosis of adenomyoma made previous to operation. The clinical diagnosis was clothed in such terms as fibromyoma or pelvic tumor, both of which diagnoses show recognition of definite pathologic conditions of a neoplastic nature without attempting to specify in terms of detailed pathology.

The condition as related to years is as follows:

YEAR	MYOMAS	ADENOMYOMAS	ADENOMYOMAS IN FALLOPIAN TUBE
1907.....	150	0	0
1908.....	154	6 (3.8 per cent)	0
1909.....	198	6 (3 per cent)	0
1910.....	213	8 (3.7 per cent)	0
1911.....	228	18 (7.8 per cent)	0
1912.....	231	12 (5.1 per cent)	0
1913.....	274	21 (7.7 per cent)	0
1914.....	316	22 (6.9 per cent)	0
1915.....	348	23 (6.5 per cent)	0
1916.....	386	37 (9.5 per cent)	3
1917.....	378	36 (9.5 per cent)	1
1918.....	301 (to Oct. 1)	22 (7.3 per cent)	1
	3177 211	211 (6.43 per cent)	5
Total.....	3388		

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# CLINICAL EFFICIENCY AND TERMINOLOGY IN CANCER OF THE BREAST\*

W. C. MACCARTY AND H. M. CONNER

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In spite of the fact that cancer of the breast has been abundantly and excellently considered by the best authorities over a long period of years, there are some reasons why it demands renewed interest.

Besides the pathologic facts, there are four parties concerned, from the standpoint of efficiency, in dealing with this condition, which is of such economic and humanitarian importance. Each party represents a different degree of opportunity to handle facts relative to diagnostic probability and certainty. The one with the least certainty and fewest facts is the patient, the one with the most facts and greatest certainty is the pathologist; the clinician and surgeon are the intermediaries between these two. Perhaps this statement will not be accepted immediately by clinicians and surgeons, both of whom in the absence of clinically inclined pathologists have, of necessity, been forced to assume the rôle of clinician and pathologist, the first and last courts.

A combined clinician, surgeon, and pathologist would be an ideal individual, and such an one was possible a few years ago, when clinical knowledge, surgical experience, and pathologic facts were limited. To-day each represents specialism in the field of medical science the many branches of which have grown to such proportions that no one person can comprehend all the clinical facts, perform efficiently all operations or master the subject of pathology completely. Each must know all the facts concerning his own subject and all must know enough of relationships to assist in the correlation of the knowledge of all specialists.

Since cancer of the breast starts as a microscopic condition for which no specific cure has been discovered, especially in its grossly recognizable stages, it possesses important significance long before it becomes possible for the patient, clinician, surgeon, or pathologist to recognize its presence by any known methods. From the standpoint of gross diagnosis of the early presence of the condition in the patient, all parties

\*Reprinted from Surg., Gynec. and Obst., 1919.

deal only with probabilities which approach certainty usually in direct proportion to the size of the growth or its fixity to the skin or underlying muscles. Fixity, however, is not absolute as active clinicians, surgeons and pathologists know.

A comparative study of pre-operative clinical and pathologic diagnoses reveals the following facts relative to the clinician's diagnosis in relation to cancer of the breast in two large series:

	FIRST SERIES	SECOND SERIES
Number of breasts removed.....	1800	300
Number of positive pre-operative clinical diagnoses.....	1526 (84.8 per cent)	217 (72 $\frac{1}{3}$ per cent)
Number of doubtful pre-operative clinical diagnoses.....	274 (15.2 " " )	83 (27 $\frac{2}{3}$ " " )
Number of positive pre-operative diagnoses correct regarding malignancy or benignancy.....	1146 (75.0 " " )	199 (91.7 " " )
Number of positive pre-operative diagnoses incorrect regarding malignancy or benignancy.....	380 (25.0 " " )	18 ( 8.3 " " )
Number of expressed positive diagnoses of malignancy correct regarding malignancy.....	725 (94.2 " " )	111 (94.9 " " )
Number of expressed positive diagnoses of malignancy incorrect regarding malignancy or benignancy.....	44 ( 5.8 " " )	6 ( 5.1 " " )
Number of expressed doubtful diagnoses of malignancy correct regarding malignancy or benignancy.....	93 (58.0 " " )	21 (67.7 " " )
Number of expressed doubtful diagnoses of malignancy incorrect regarding malignancy or benignancy.....	68 (42.0 " " )	10 (32.3 " " )
Number of expressed positive diagnoses of benign conditions correct regarding malignancy or benignancy.....	421 (91.0 " " )	91 (86.6 " " )
Number of expressed positive diagnoses of benign conditions incorrect regarding malignancy or benignancy.....	41 ( 9.0 " " )	14 (13.4 " " )
Number of expressed doubtful diagnoses of a benign condition correct regarding malignancy or benignancy..	10 (77.0 " " )	13 (86.6 " " )
Number of expressed doubtful diagnoses of a benign condition incorrect regarding malignancy or benignancy..	3 (23.0 " " )	2 (13.4 " " )
Number of diagnoses of nodule, tumor or mass or no diagnosis.....	395 (22.0 " " )	39 (13.0 " " )
Number of these malignant.....	69 (17.5 " " )	7 (17.9 " " )
Number of positive diagnoses of malignancy.....	769 (42.6 " " )	117 (39.0 " " )
Number of doubtful diagnoses of malignancy.....	161 ( 8.95 " " )	31 (10.33 " " )
Number of carcinomas in laboratory....	933 (51.83 " " )	148 (49.33 " " )
Number of carcinomas not diagnosed positively by clinician.....	208 (22.3 " " )	37 (24.2 " " )
Of malignancy the clinician diagnoses with certainty only.....	725 (77.7 " " )	111 (75.0 " " )
Of those not diagnosed positively the clinician has expressed suspicion in ..	93 (44.5 " " )	21 (57.0 " " )

Two series were studied for the purpose of determining statistically elements of certainty and probability in clinical diagnosis from a clinologic standpoint in relation to pathologic facts and terminology. The first series<sup>a</sup> represents the first 1800 cases and the second series the last 300 cases which have come under observation. The pre-operative diagnoses or instructions to the surgeons were made by clinicians whose experience ranged from five to twenty-five years, and whose training had been obtained in the representative medical schools of the United States and Canada, and, in some instances, the leading institutions of Europe.

From these studies the following generalizations may be made relative to actual clinical efficiency when endeavoring to differentiate all malignant conditions from all benign conditions in the breast:

	SECOND SERIES	FIRST SERIES
1. General positive diagnoses are relatively fewer than formerly . . . . .	72.0 per cent	84.8 per cent
2. Correctness of general positive pre-operative diagnoses is relatively greater than formerly . . . . .	91.7 " "	75.0 " "
3. Correct, expressed, positive diagnoses of malignancy remain practically the same . . . . .	94.9 " "	94.2 " "
4. Expressed doubtful diagnoses of malignancy are more correct than formerly . . . . .	67.7 " "	58.0 " "
5. Correct, expressed positive diagnoses of a benign condition remain about the same . . . . .	86.0 " "	91.0 " "
6. Expressed doubtful diagnoses of a benign condition are more frequent than formerly . . . . .	86.6 " "	77.0 " "
7. Diagnoses of "tumor," "mass," "nodule," or "no diagnosis" are fewer than formerly . . . . .	13.0 " "	22.0 " "
8. Of all breast conditions the clinician makes a positive diagnosis of malignancy in about the same percentage . . . . .	39.0 " "	42.6 " "
9. Operable carcinomas occur in about the same relative frequency . . . . .	49.3 " "	51.8 " "
10. The clinician makes a doubtful diagnosis in all carcinomas more frequently than formerly . . . . .	21.0 " "	17.2 " "
11. His certain diagnosis of malignancy remains about the same . . . . .	75.0 " "	77.7 " "
12. Of those cases of malignancy not positively diagnosed he expresses a suspicion in a greater percentage than formerly . . . . .	57.0 " "	44.5 " "
13. Of the last 300 breasts operated on, specimens of 21 (7 per cent) were submitted to the laboratory for diagnosis before the complete operation was performed.		

Although these figures vary slightly from time to time, the fundamental facts relative to diagnostic certainty remain the same. Clinicians and surgeons are dealing with fairly definite percentages of certainty and probability, the former of which will become less and less as the



layman and clinician become educated to the recognition of pathologic although indefinite conditions.

The factors of uncertainty in clinical and even gross diagnosis are emphasized in the following statistics which show the necessity of microscopic diagnosis after specimens have been removed from the body.

Total number of general pathologic diagnoses recorded between August 1, 1917, and December 1, 1918, 11,236.

Percentage of diagnoses which were of necessity microscopic, 22 per cent.

The breast presents a smaller figure for necessary microscopic diagnosis than do general specimens, the former being 13.3 per cent.

The efficiency of pathologic terminology when utilized as clinical terminology in diagnosing mammary conditions is seen in the following list of positive pathologic mistakes which occurred in the series of 1800 cases:

PATHOLOGIC DIAGNOSIS		CLINICAL DIAGNOSIS
Diffuse lipoma	called	chronic mastitis
Cyst	"	fibro-adenoma
Fibro-adenoma	"	adenoma
Fibromyxoma	"	carcinoma
Adenofibroma	"	fibro-adenoma
Fibro-adenoma	"	retention cyst
Fibro-adenoma	"	adenofibroma
Adenofibroma	"	carcinoma
Fibro-adenoma	"	fibroma
Cystic fibro-adenoma	"	myxoma
Adenofibroma	"	chronic mastitis
Cystic fibro-adenoma	"	chronic mastitis
Cysts	"	carcinoma
Cysts	"	chronic mastitis
Fibro-adenoma	"	chronic mastitis
Intracanalicular fibroma	"	carcinoma
Lipoma	"	cyst
Papillary fibrocystadenoma	"	cystadenoma
Cyst	"	adenoma (early carcinoma)
Fibro-adenoma	"	cystadenoma
Cystadenoma	"	adenoma
Adenofibroma	"	fibroma
Intracanalicular papilloma	"	chronic mastitis
Intracanalicular fibro-adenoma	"	fibroma
Fibrolipoma	"	chronic mastitis
Intracanalicular fibro-adenoma	"	adenoma
Adenofibroma	"	cystadenoma
Fibro-cystadenoma	"	adenoma
Intracanalicular fibro-adenoma	"	fibro-adenoma
Intracanalicular fibro-adenoma	"	chronic mastitis
Myxoma	"	neuroma
Intracanalicular adenofibroma	"	fibroma
Cyst	"	adenoma
Adenomyxoma	"	adenoma
Lipoma	"	fibroma

In the same series of 1800 specimens the following pathologic names were applied by the pathologists to the conditions found:

Adenofibroma	* Fibrolipoma
Adenoma	* Fibromyoma
* Adenomyxofibroma	* Fibrocystadenoma
* Angioma	* Fibromyxo-adenoma
* Adenofibromyxoma	* Intracanalicular myxoma
* Adenomyxoma	* Intracanalicular fibroma
Benign	* Intracanalicular fibro-adenoma
Cyst	* Intracanalicular adenofibroma
* Cystic fibroma	* Intracanalicular papilloma
Cystadenoma	* Intracanalicular fibromyxoma
* Chondrolipofibroma	* Intracystic papilloma
Cystic fibro-adenoma	* Intracanalicular myxofibroma
Cystic adenofibroma	* Intraductal papilloma
* Calcareous tumor	* Intracanalicular adenomyxoma
Chronic mastitis	* Intracanalicular fibro-adenomyxoma
* Cystic intracanalicular papillary adeno- fibroma	* Intracanalicular papilloma (malignant)
* Calcareous adenoma	Lipoma
* Cystic calcareous fibroma	* Myxofibroma
* Calcareous intracanalicular adenofibroma	* Myxofibro-adenoma
Carcinoma	Myxoma
* Dermoid	* Myxo-adenofibroma
* Embryoma	* Papillary cyst
Fibro-adenoma	* Papillary fibro-adenoma
Fibroma	* Papillary fibrocystadenoma
Fibromyxoma	* Pericanalicular fibroma
	Sebaceous cyst

\* Pathologic terms not utilized by the clinician.

The clinician, however, applied the following more limited list of names, a fact which shows his own recognition of his inability to diagnose in terms of pathologic terminology:

Adenoma	Growth
Adenofibroma	Lipoma
Lipoma	Lump
Benign	Myxoma
Cyst	Mass
Carcinoma	Malignant
Chronic mastitis	Nodule
Cystic fibro-adenoma	Neuroma
Cystadenoma	No diagnosis
Cystic degeneration	Papilloma
Fibroma	Plaque
Fibro-adenoma	Retention cyst
Sarcoma	Sebaceous cyst
Fibromyxoma	

The terms utilized by both the clinician and the pathologist represent their code of communication of ideas which has been culled out of many text-books and articles which have come to them during their medical training or during their experience as practitioners. In view of the fact that there has been no uniformity of code utilized by the many practitioners with whom we have been associated the question of economic

and scientific efficiency of our present pathologic terminology has become one of importance.

The following lists of pathologic terminology have been obtained from such standardized texts as those of Kaufmann, Adami, Delafeld and Prudden, Hertzler, Aschoff, Ziegler, and MacCallum. In the lists all pathologic conditions are named and listed because all conditions must be differentiated from malignant conditions of which carcinoma certainly is the most prominent.

**KAUFMANN:**

Parenchymatous mastitis  
 Infectious mastitis  
 Mastitis infectiosa parenchymatosa  
 Mastitis infectiosa interstitialis  
 Chronic mastitis (mastitis chronica cystica)  
 Cirrhosis mammae  
 Cyst  
 Maladie cystique de la Mamelle (Reclus)  
 Cystadenoma  
 Polycystoma  
 Intracanalicular cystadenoma  
 Mastitis tuberculosa obliterans  
 Mastitis gummosa  
 Lipomatosis  
 Adenoma  
 Fibro-adenoma  
 Adenofibrosom  
 Adenofibroma  
 Fibro-epithelial tumors  
 Adenomyxoma  
 Adenosarcoma  
 Fibroma  
 Myxoma  
 Sarcoma  
 Adenosarcoma  
 Fibro-adenoma acinosum  
 Fibro-adenoma tubulare  
 Fibroma pericanaliculare  
 Plexiform fibroma  
 Pericanalicular fibromyxoma  
 Fibromyxosarcoma  
 Fibro-adenoma cysticum  
 Intracanalicular fibroma  
 Intracanalicular myxoma  
 Intracanalicular sarcoma  
 Fibroma intracanaliculare mammae oedematosum  
 Cystosarcoma  
 Cystosarcoma phyllodes  
 Fibroma proliferum or arborescens  
 Myxoma proliferum or arborescens  
 Sarcoma proliferum or arborescens  
 Fibroma } Papillare or polyposum  
 Myxoma } intracanaliculare  
 Sarcoma }  
 Cystadenoma papilliferum  
 Intracanalicular cystadenoma

**KAUFMANN (Continued):**

Cystic papillary epithelioma  
 Papillary cystocarcinoma  
 Papillary epithelioma (cylinder cell)  
 Papillary carcinoma  
 Fibromyxoma  
 Myoma  
 Myofibroma  
 Cavernous hæmangioma  
 Enchondroma  
 Osteoma  
 Osteochondroma  
 Lipoma  
 Small round-cell sarcoma  
 Spindle cell sarcoma  
 Polymorphic cell sarcoma  
 Giant-cell sarcoma  
 Angiosarcoma  
 Endothelioma  
 Chondrosarcoma  
 Osteoid sarcoma  
 Sarcocarcinoma  
 Chondrosarcocarcinoma  
 Carcinoma chondrosarcomatosum  
 Cystic papillary adenocarcinoma  
 Paget's disease  
 Carcinoma solidum  
 Adenocarcinoma  
 Flat-cell carcinoma  
 Carcinoma solidum simplex  
 Tubular carcinoma  
 Acinous carcinoma  
 Carcinoma solidum medullare  
 Carcinoma granulosum  
 Carcinoma solidum scirrhosum  
 Cancer atrophicans  
 Medullary carcinoma  
 Carcinoma simplex  
 Psammocarcinoma  
 Carcinoma colloides  
 Carcinoma gelatinosum  
 Carcinoma cysticum  
 Carcinoma cylindromatosum  
 Adenocarcinoma cylindromatosum  
 Cystocarcinoma papillare  
 Cystocarcinoma simplex  
 Cystocarcinoma papilliferum  
 Carcinosarcoma  
 Carcinochondrosarcoma

**MANN (Continued):**

Cystoma  
 Cancer en cuirasse  
 St  
 Evolution cysts  
 Lactocoele  
 Dermoid cyst  
 Epidermoidal cyst  
  
**MI:**  
 Angioneurotic edema forming lumps in breast  
 Retro-mammary abscess  
 Acute mastitis  
 Periperal mastitis  
 Diffuse mastitis  
 Interlobular mastitis  
 Acute galactophoritis  
 Chronic mastitis  
 Sclerosis mammae  
 Mastitis carcinomatosa  
 Acute miliary tuberculosis  
 Discrete tuberculosis  
 Confluent tuberculosis  
 Chancre  
 Gumma  
 Diffuse mastitis (syphilitic)  
 Actinomycosis  
 Cyst  
 Hypertrophy  
 Diffuse hypertrophy  
 Cystadenoma  
 Retention or simple cyst  
 Adenoma  
 Fibroma  
 Adenofibroma  
 Fibro-adenoma  
 Adenomyxoma  
 Adenosarcoma  
 Myxo-adenoma  
 Sarco-adenoma  
 Lipoma  
 Myxoma  
 Myoma  
 Angioma  
 Osteoma  
 Chondroma  
 Epithelioma  
 Carcinoma  
 Sarcoma  
 Plexiform fibroma  
 Pericanalicular fibroma  
 Periglandular fibroma  
 Intracanalicular fibroma  
 Fibroma cysticum  
 Cystadenofibroma intracanalicular  
 Adenocoele  
 Cholesteatoma  
 Adenoma-acinosum  
 Adenoma tubulare  
 Solid sarcoma  
 Cystic sarcoma  
 Angiosarcoma

**ADAMI (Continued):**

Perithelioma malignum  
 Melanotic sarcoma  
 Round-cell sarcoma with striated muscle  
 Cystosarcoma phyllodes  
 Squamous epithelioma  
 Paget's disease  
 Malignant papillary dermatitis  
 Superficial carcinoma of skin  
 Acute miliary carcinosis  
 Scirrhus carcinoma  
 Carcinoma simplex  
 Carcinoma medullare  
 Adenocarcinoma  
 Cystic carcinoma  
 Cancer atrophicus  
 Encephaloid carcinoma  
 Carcinoma gelatinosum  
 Cystadenocarcinoma  
 Cancer en cuirasse  
 Panzerkrebs  
 Echinococcus cyst  
 Dermoid cyst  
 Cysticercus  
 Galactocoele

**DELAFIELD AND PRUDDEN:**

Paget's disease  
 Suppurative mastitis  
 Acute exudative mastitis  
 Tuberculosis of mamma  
 Chronic mastitis  
 Cystic hyperplasia  
 Syphilitic ulcers  
 Hypertrophy of mamma  
 Fibroma  
 Intracanalicular fibroma  
 Intracanalicular fibro-adenoma  
 Pericanalicular fibroma  
 Myxoma  
 Osteoma  
 Chondroma  
 Osteochondroma  
 Lipoma  
 Myoma  
 Angioma  
 Adenoma  
 Papillary cystadenoma  
 Sarcoma  
 Carcinoma  
 Medullary carcinoma  
 Scirrhus carcinoma  
 Gelatinous carcinoma  
 Epithelioma

**HERTZLER:**

Adenofibroma  
 Fibro-adenoma  
 Intracanalicular adenofibroma  
 Chronic interstitial mastitis  
 Senile parenchymatous hypertrophy  
 Schimmelbusch's disease  
 Tuberculosis

**HERTZLER (Continued):**

Mixed tumors  
Cystic sarcoma  
Adenosarcoma  
Cystosarcoma  
Sarcoma myxomatodes  
Chondrosarcoma  
Sarcoma phyllodes.  
Sarcoma  
Lipoma  
Papilloma  
Myxoma  
Angioma  
Chondroma  
Osteoma  
Atheromatous cysts  
Carcinoma  
Scirrhus carcinoma  
Medullary carcinoma  
Encephaloid carcinoma  
Carcinoma simplex  
Carcinoma en cuirasse  
Glandular carcinoma  
Acute encephaloid carcinoma  
Lactation cancer  
Paget's disease  
Colloid carcinoma

**ASCHOFF:**

Fibro-adenoma  
Fibro-adenoma pericanaliculare  
Fibro-adenoma intracanalicular  
Adenomixofibroma  
Adenolipofibroma  
Adenofibrosarcoma  
Cystadenosarcoma phyllodes  
Solid adenoma  
Cystadenoma papilliferum  
Involution cyst  
Mastitis cystica chronica  
Carcinoma  
Carcinoma en cuirasse  
Carcinoma medullare  
Carcinoma scirrhosum  
Psammo carcinoma  
Colloid carcinoma  
Paget's disease (epithelioma of nipple)  
Melanoma  
Fibroma  
Sarcoma  
Chondroma  
Osteoma  
Endothelioma  
Perithelioma

**ZIEGLER:**

Mastitis

**ZIEGLER (Continued):**

Perimastitis  
Cysts  
Hypertrophy  
Adenoma mammae  
Adenoma acinosum  
Adenoma tubulare  
Adenofibroma  
Fibroma pericanaliculare  
Fibroma intracanalicular  
Adenocystoma  
Adenocystoma papilliferum  
Cystoma  
Fibroma phyllodes  
Sarcoma phyllodes  
Adenomixofibroma  
Adenosarcoma  
Endothelioma  
Fibrosarcoma  
Myxosarcoma  
Intracanalicular fibrosarcoma  
Adenocarcinoma  
Lipoma  
Angioma  
Chondroma  
Osteochondroma  
Osteosarcoma  
Cystocarcinoma mammae papilliferum  
Acinous cancer  
Tubular scirrhous cancer  
Cystocarcinoma  
Carcinoma simplex  
Carcinoma medullare  
Carcinoma acinose  
Carcinoma tubulare  
Cancer en cuirasse  
Paget's disease  
Psammocarcinoma

**MACCALLUM:**

Carcinoma  
Paget's disease  
Medullary cancer  
Scirrhus cancer  
Adenocarcinoma  
Comedo cancer  
Colloid carcinoma  
Cancer en cuirasse  
Chronic cystic mastitis  
Adenoma  
Adenofibroma  
Intracanalicular fibro-adenoma  
Intracystic papilloma  
Intracanalicular myxofibroma  
Mixed tumors  
Sarcoma

The very fact that there is no definite uniformity in the pathologic terminology is evidence of the fact that pathologists themselves are not perfectly clear in their own minds relative to conditions which they

attempt to handle, that is, pathologic conditions in the breast. At least they have not gotten together in order to unify conceptions and terminology. This has led to great confusion for the clinician.

In view of the facts, herewith presented, relative to clinical diagnostic and pathologic terminologic efficiency it seems necessary to present a scheme of terminology which represents greater efficiency, not only from the standpoint of biopathologic facts on which the new terminology is essentially based, but also from the standpoint of clinical efficiency.

It is not necessary to review in detail the anatomy of the breast in order to state the fundamentals which underlie a simple conception of our subject. In so far as carcinoma, from which all other conditions must be differentiated and which represents the majority of malignant conditions, is concerned the breast consists of certain definite tissues—that is, epitheliotex of the skin, modified epitheliotex of the ducts and sinuses, and adenotex lining the acini which are the structural and functional mammary units (Fig. 163). Each of these tissues rests upon cells which have been demonstrated to be reserve cells for their regeneration. These reserve cells have been termed epithelioblasts and adenoblasts respectively.<sup>7</sup> These three and these three tissues only and their respective regenerative cells are concerned in the question of carcinoma and epithelioma of this organ. Since epithelioma of the breast is a rare condition and presents itself as a superficial lesion which attracts attention early and is easily diagnosed, it is of little importance in comparison to the subject of carcinoma, which is the main subject under consideration. We are interested, for the present, only in the modified epitheliotex of the ducts or tubules and the adenotex lining the acini with their respective regenerative cells.

For the sake of those of the profession who still rely upon their gross diagnosis it must be emphasized that these tissues are composed of microscopic cells and any changes occurring which involve a dozen or perhaps more of such cells would escape the notice of the most experienced gross pathologist although he might be assisted by a hand lens.

From a practical standpoint the question arises: What is the smallest carcinoma which can be positively recognized clinically? This is, in our experience, an unanswerable question because neoplasms in the breast are associated with many variable conditions; some breasts contain much fat; others contain little fat; some neoplasms are near the skin or pectoral muscle and some are in other portions of the organ.

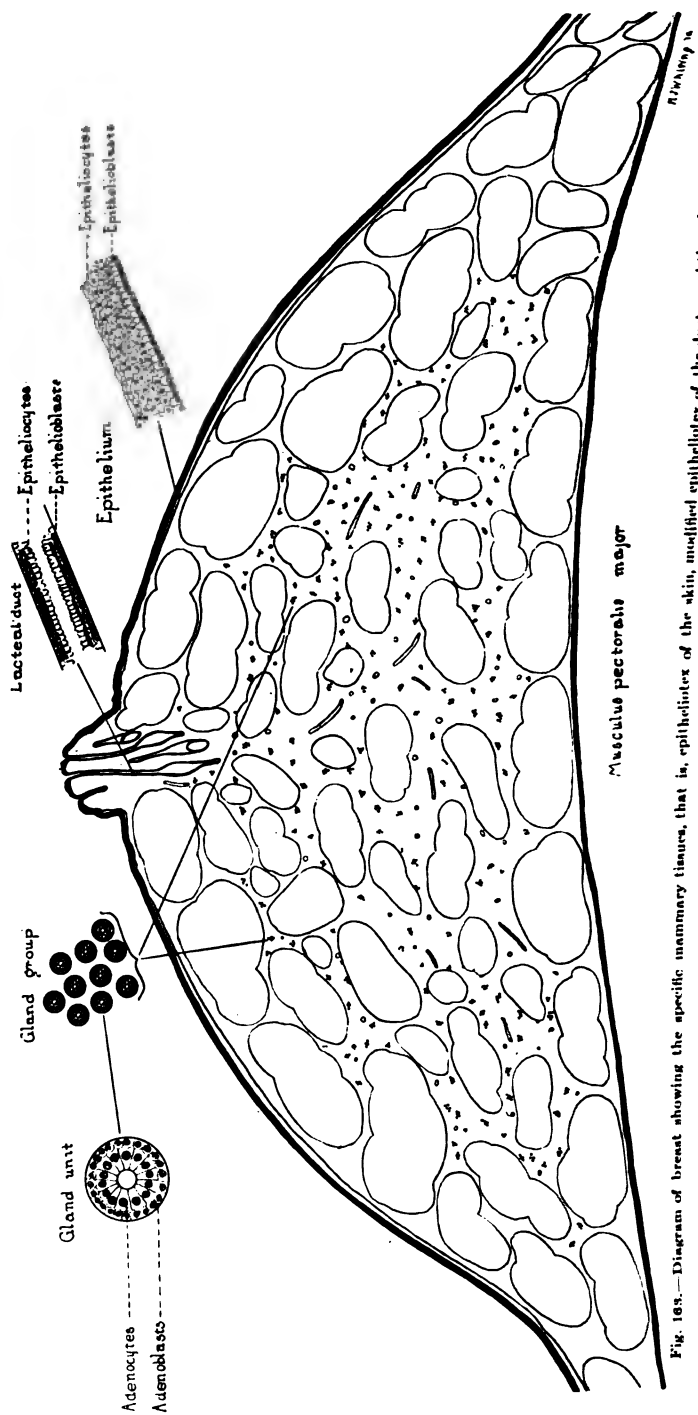


Fig. 108.—Diagram of breast showing the specific mammary tissues, that is, epithelium of the skin, modified epithelium of the ducts, and the acini of the acini

There certainly is no point of selection for the development of such conditions. We know of nothing in a clinical history which will differentiate a carcinoma five millimeters in diameter from an encapsulated fibro-adenoma or a cyst of equal diameter. Multiplicity of lesions, while of some importance, is in no way positive because carcinomas are sometimes multiple, fibro-adenomas if multiple or single may also be associated with carcinoma and cysts not infrequently are either associated with carcinomas or contain papillomas which are sometimes malignant. The best that a clinician can possibly do is to consider all possibilities. If he operates on probabilities or what he considers certainties his error may, in a fairly definite number of cases, be one of too radical or one of insufficient operation, or he may leave a carcinomatous condition in the rest of the breast.

If carcinoma were the only condition which arises in the breast, our problems would be less difficult, but the fact that the organ consists of other tissues, fibrotex, myotex, endotheliotex, neurotex, and lipotex, complicates our relations to neoplastic possibilities. Each of these tissues and the adenotex of the ducts and acini are subject to benign and malignant conditions. These are the tissues which play rôles in any regenerative process. All other tissue-cells, such as leukocytes, lymphocytes, and erythrocytes, which are found during this process, are migrants coming to this organ through the blood-stream.

Fundamental mammary tissues possess the power of regeneration, the degree of which varies with the tissue, myotex, and neurotex possessing the least if any regenerative power.

Regeneration rests in the reserve cells which have been called

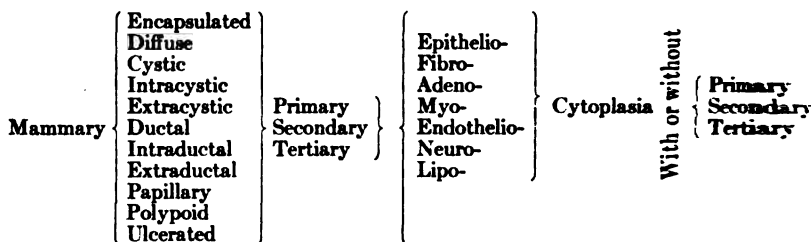
Epithelio-	} blasts.*
Fibro-	
Adeno-	
Myo-	
Endothelio-	
Neuro-	
Lipo-	

These cells react biologically in three degrees to any chronic destructive force or thing.<sup>7</sup> The first reaction is hypertrophy, the second is hyperplasia, and the third is migration. These are fundamental biologic reactions, manifestations of which produce microscopic, gross, and clinical pictures, and their recognition is dependent on the efficiency of our natural and artificial instruments of observation.

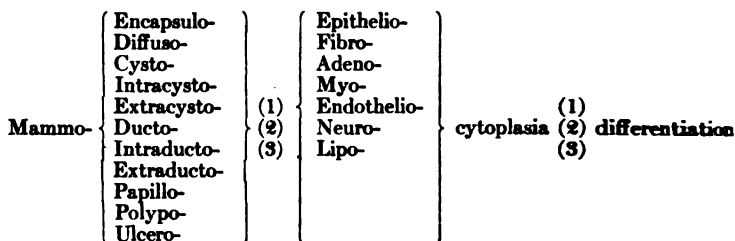
\* Endotheliocytes probably are so primitive that they are themselves endothelioblasts.



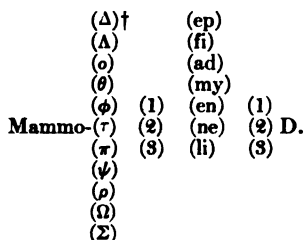
The anatomic location of the biologic reactions, their gross and microscopic structural manifestations, and their clinical behavior may be briefly expressed as follows:<sup>7</sup>



This terminology may be abbreviated in the following manner:



If one desires to express the facts symbolically, this may be done as follows:



\* Differentiation has been divided into three degrees, as follows: First degree: The normal tissue alignment of cells. Second degree: The normal tissue alignment of cells plus normal polarity of cells. Third degree: The normal tissue alignment plus normal polarity plus normal morphologic cyto characteristics.

† The Greek letters have the following symbolic meaning:

- Δ delta = circumscribed or encapsulated
- Δ lambda = diffuse or non-encapsulated
- o omicron = cystic
- θ theta = intracystic
- φ phi = extracystic
- τ tau = ductal
- π pi = intraductal
- ψ psi = extraductal
- ρ rho = papillary
- Ω omega = polypoid
- Σ sigma = ulcerated

## DUCTLESS GLANDS



# THE BLOOD PICTURE IN EXOPHTHALMIC GOITER\*

W. A. PLUMMER

The present report is based on the study of the blood counts in 578 patients with exophthalmic goiter who were examined in the Mayo Clinic during the years 1912 and 1913. To obtain the mortality statistics a larger series of cases was studied and individual investigations were made of those cases which showed marked variations from the average. The count from the entire group is as follows:

Hemoglobin.....	83.1 per cent
Erythrocytes.....	4,790,000
Leukocytes.....	6,973.5
Polymorphonuclears (relative).....	58.3
Polymorphonuclears (absolute).....	4,063.5
Small lymphocytes (relative).....	34.8
Small lymphocytes (absolute).....	2,426.7
Large lymphocytes.....	4.4
Transitionals.....	1.1
Eosinophiles.....	1.6
Basophiles.....	.49

The figures above the differential count are well within normal limits. There is a relative and an absolute mononucleosis and a percentage decrease in the polymorphonuclear neutrophils. The eosinophiles are slightly under the normal average. We found that the hemoglobin was below 70 per cent in only 13 (2.2 per cent) of the 578 patients. The average for this group is 62 per cent, while 44 is the lowest individual percentage. Considering the degree of organ degeneration frequently present in this disease there are surprisingly few patients with even a low-grade anemia. The divergence from the normal in the numeric relationship between neutrophilic and small lymphocytic cells was studied as follows: The 25 counts having the least number of leuko-

\* Presented before the Minnesota State Medical Association, August, 1918, Duluth, Minn. Reprinted from Minn. Med., 1919, ii.

cytes and the 25 having the greatest number were placed in separate columns. The averages for the first group are:

Leukocytes.....	3364
Polymorphonuclears (relative).....	50.9
Polymorphonuclears (absolute).....	1712.3
Small lymphocytes (relative).....	42.7
Small lymphocytes (absolute).....	1436.4

If 1500 is taken to represent the normal total small lymphocyte count, it will be found that, in spite of a marked leukopenia, the absolute count will still be within normal limits. On the other hand, the total number of neutrophils has been reduced to 1712.3, or over 3000 less than the normal average. These numbers show that when a leukopenia is present in cases of exophthalmic goiter, it is the result of a decrease in the total number of polymorphonuclear neutrophils. The averages in the second group are:

Leukocytes.....	12872
Polymorphonuclears (relative).....	66.6
Polymorphonuclears (absolute).....	8572.7
Small lymphocytes (relative).....	27
Small lymphocytes (absolute).....	3475.4

These figures show the same relationship between neutrophils and small lymphocytes, but to a lesser degree. In other words, the higher the total white count, the less the divergence from normal in the individual relative counts. These patients gave no evidence of having an acute infection at the time the blood was examined.

The two questions which confronted us were: First, what are the factors which determine these variations, and, second, what is their diagnostic and prognostic significance?

It was natural to assume that the early cases would show a lymphocyte count more nearly normal. Four hundred and eighty cases in which the patients had had symptoms for twenty-four months or less were arranged into twelve groups. In the first were placed the counts of those patients who had noticed symptoms for two months or less; in the second those who had had symptoms for from two to four months, and so on in two month intervals up to twenty-four months, which represented the twelfth group. The first group gave averages as follows:

Leukocytes.....	6179.7
Small lymphocytes (relative).....	34.3

In the twelfth, in which the symptoms had continued from twenty-two to twenty-four months, the averages were:

Leukocytes.....	7051.7
Small lymphocytes (relative).....	34.7

It is unnecessary to give the averages for the intervening groups, as the counts are parallel to those given. Although there are not so many leukocytes in Group I as there are in Group XII, this fact has no significance in the light of a detailed study of the entire series. There is nothing to show that the duration of symptoms bears any relationship to the degree of lymphocytosis.

It would seem that the degree of lymphocytosis should be directly proportional to the severity of the symptoms. We tried to prove this by regrouping the blood counts from several angles. The counts from the patients whose symptoms were marked, and were recorded as showing a present severity of  $3\frac{1}{2}$  or 4 on a basis of 1 to 4, were averaged separately, with the following results:

Leukocytes.....	6400
Small lymphocytes (relative).....	34.9

The variation from the total averages is very slight. We also studied the case histories of the patients having a lymphocyte percentage below 20 and those having a percentage above 45, but were unable to show that one group represents a greater degree of hyperthyroidism than the other.

As the patients who died, either following surgical interference or otherwise, on the whole suffered a high degree of hyperthyroidism, their counts were averaged. From 1909 to 1914 inclusive there were 54 surgical and non-surgical deaths among the patients having had complete blood examinations. The averages were:

Leukocytes.....	7320.9
Small lymphocytes (relative).....	31.3

To eliminate from this group, as far as possible, all patients except those dying of acute hyperthyroidism, we excluded those having had complications, such as pneumonia, acute nephritis, etc., and obtained the following averages:

Leukocytes.....	7917
Small lymphocytes (relative).....	32

We find from these studies that neither the leukocyte count nor the degree of mononucleosis is dependent on the severity of the symptoms and that they cannot be used as a guide in prognosis.

In 83 patients who had cardiac dilatation of one inch or more to the left, the averages were:

Leukocytes.....	6730.7
Small lymphocytes (relative).....	35.2

and in the patients who had cardiac edema there were:

Leukocytes.....	6309
Small lymphocytes.....	36.3

Evidently the characteristic picture is not influenced by cardiac damage.

Seventy-four counts made from one to three weeks after thyroidectomy showed the following averages:

Leukocytes.....	8633
Small lymphocytes.....	34.5

Except for a slight increase in the number of leukocytes, which may be accounted for by the recent operation, no variation is shown; also except for the leukocytosis, which may be present the first few days following operation, thyroidectomy does not influence the blood picture during the first three weeks following operation.

Averages show that neither sex nor age affects the degree of mononucleosis.

During long periods patients suffering from hyperthyroidism have abnormal appetites, but, on the other hand, for days or weeks they may eat less than normal. As digestion often influences the leukocyte formula, 40 patients were examined with reference to the bearing this might have on the blood count. In each instance the blood was taken before breakfast and again about two hours after a heavy meal; there was no material change in the relative counts.

That the average percentage of small lymphocytes is well above normal would indicate that at least the count is of some diagnostic value. In this connection it may be noted that of the 578 patients examined, 5 had a relative count of 15 or below; 39 had a relative count of from 15 to 20; 169 had a relative count of from 20 to 30; 212 had a relative count of from 30 to 40, and 162 had a relative count above 40. Only 7.5 per cent had a small lymphocyte count of 20 or below. It will be seen that a count below 20 is of some negative value while one above 40 is of positive value. Intermediate readings are of less significance because of the wide fluctuation among normal counts.

#### CONCLUSIONS

Although some writers still maintain that anemia of the chlorotic type is a characteristic of the disease, this is neither borne out by our findings nor by those published by Kocher. An anemia, when present, is neither the result of, nor necessarily coincident with, hyperthyroidism.

but is due to secondary changes. Kocher has emphasized the presence of a leukopenia and has based his conclusions on 106 cases in which there was an average count of about 5000 leukocytes. Our series had an average of 6973.5, and it would seem that the real status in regard to the number of leukocytes in patients with exophthalmic goiter is that there is a wider variation, probably dependent on the neutrophiles, than among normal counts, and while there are more counts showing a decrease in leukocytes there are an equally large number showing a slight increase. We have not been able to demonstrate that a leukopenia is more frequently present in the early stages of the disease.

We agree with Kocher and others who have confirmed his work that in the majority of the cases there is a relative and absolute mononucleosis; and that when a leukopenia is present the decrease takes place at the expense of the neutrophiles; we have also found that the converse is true to a lesser degree. The eosinophiles show some variation, but the total averages give no increase. In our mortality statistics the relative lymphocyte count is a few points under the average for the entire series, but it is not sufficient to be of value in prognosis. The differential count is of limited value in diagnosis. Except for a polymorphonuclear leukocytosis immediately following operation, and during tonsillitis and other acute infections, we have been unable to determine any factor which influences the characteristic blood picture. There are two points that may explain our inability to determine the influences which sway the count.

1. There is much to indicate that the changes in the leukocyte formula are owing to two more or less independent variables—one which causes a lymphocytosis and another which influences the neutrophilic count. The first may be found in a hyperplasia of the lymphoid tissues, and the second, as Falta has pointed out, in a fluctuating abnormal distribution of the neutrophiles in the vascular tree.

2. Until recently we have not determined the metabolic rate, and as a result there have been errors in marking the degree of hyperthyroidism. Much may be gained, especially in individual cases, with their varying rates, by examining the blood coincident with the metabolic readings and pulse pressures.



# THE THYROID HORMONE AND ITS RELATION TO THE OTHER DUCTLESS GLANDS\*

E. C. KENDALL

Much of the research work concerning the ductless glands has been from the viewpoint of relating some one gland to some particular portion or restricted function of the body. Thus, the pituitary has been associated with the growth of the bones and certain skeletal formations; the thyroid has been associated with the nerves, and some writers have satisfied themselves that the activity of certain ductless glands is explained by clinical syndromes wherein only portions of the body show abnormalities. There have been relations suggested which were based on embryologic grounds. Organs and tissues derived from some common source have been supposed to be more or less related in function. Some of the most elaborate relationships of the ductless glands are based on histologic findings. The vast amount of research work that has been done with this object in view has indeed told us a great deal concerning the relationships of the ductless glands to certain bodily functions, but beyond this knowledge one cannot penetrate without new tools, and without applying quantitative determinations to the physiologic processes involved.

Before the chemical balance came into existence, the alchemist held sway over the theories of matter and the relationships existing between chemical substances. The phlogiston theory was unassailable on any ground other than quantitative analysis. From a survey of the literature today concerning the ductless glands we cannot boast of being very far out of the alchemist's age, and as yet very few investigators have approached the subject in a quantitative manner, with a realization of the actual problems existing.

For a complete analysis of the exact chemical reactions produced by this or that gland, nothing short of the actual isolation of the prod-

\* Presented before the meeting of the Association for the Study of Internal Secretions, June, 1918, Chicago. Reprinted from *Endocrinology*, 1918, ii, 81-93.

is in question can really solve the problem, and even after the chemical substances responsible for the activity of the various glands have been isolated, the interpretation of their physiologic functions requires, not only the microscope, the kymograph and the chemical laboratory, but also the application of physics, chemistry, hydraulics, and mechanics. Too much emphasis has been laid in the past on clinical and experimental conditions that are only partial expressions of a fundamental reaction which in almost every case has so far escaped detection. In the meantime these minor details have been stretched to the utmost order that they may fit the theory of the supposed function of the gland and in question.

Realizing that the function of the thyroid must be based on simple chemical reactions, and trusting in the probability that the substance producing these reactions would be stable enough to be separated, the isolation of the iodine compound occurring in the thyroid was begun by me eight years ago. During this investigation a very large amount of fresh thyroid glands has been used, and the work has been pushed in several directions so that now not only has the isolation of the substance been accomplished, but it has been analyzed, its empirical and structural formula have been determined, and its synthesis has been completed.\* The physiologic action has been studied, and a large number of patients have been treated in the clinic.

All this work has emphasized the necessity of viewing the function of any endocrine gland on the very broadest possible grounds. For example, in cretinism there is a certain characteristic expression of the face, the long bones do not grow normally, the skin is dry and scaly, the hair is scant and brittle, there is no ambition, and mental activity is very much below normal. Shall one then say that the thyroid controls the length of the long bones, the skin, the hair and the nerves? This is all true, but it does not deal with the actual function of the gland and the chemical processes involved. It is following only so far as the eye can see. In this instance quantitative studies have been directed to anatomic changes and not to physiologic processes. A change in the physiologic function is being interpreted in terms of the end result produced by the change. One almost loses sight of the fact that the thyroid is just as vitally concerned in normal conditions. To the majority of those most interested the function of the thyroid does not mean

\* Mr. Osterberg, working in our laboratory, succeeded in synthesizing a small amount of thyroxin in December, 1917. Further work is in progress.

a physiologic process based on chemical reactions, but the word brings to mind a disturbance defined in clinical terms.

According to the older view, the active constituent of the thyroid functions within the gland itself. The blood passing through the gland is purified; before it enters the gland it is toxic to the organism, and after leaving the gland it is not toxic. Others have held that the location of the activity of the substance was in and through the nervous system, that through the nerves the various thyroid manifestations were brought about and that the secretion was carried from the gland to the nerves by the blood stream.

During the past ten years Plummer has been making a very detailed study of the function of the thyroid, and he has been led to believe that the location of the active constituent of the thyroid, when it functions, is within the cells not of any particular set of organs or portion of the body, but that it is a constituent of cellular life and activity. Plummer states that the active constituent of the thyroid determines the rate at which any particular cell can produce energy, that is, it establishes the quantum of energy which any cell can produce when it is stimulated, either from within itself or from without, so that the thyroid is directly related to the production of energy within the body. He has shown that one-third of one milligram of the active constituent of the thyroid increases the basal metabolic rate one per cent in an adult weighing approximately 150 pounds. Here we have not only a definition of the function of the thyroid, but it is expressed in mathematical terms with such exactness that the number of milligrams of the substance functioning within the entire body can be estimated. It is between 23 and 50 milligrams, that is, between one-third and two-thirds of one grain.

We are still confronted with the problem of the exact chemical reactions involved, but here again a great deal of light is thrown on the problem by the chemical constitution of the active constituent of the thyroid. For reasons given hereinafter the substance has been named "Thyroxin."

When thyroxin is given to a myxedematous patient all the symptoms due to myxedema are promptly relieved. When it is given in too large amounts hyperthyroid symptoms are produced. This has been known now for more than three years, and on these grounds it has been stated that thyroxin is the active constituent of the thyroid. But the fact that a physiologic response is produced by the administration of a substance is not an explanation of the physiologic function of that substance, and

it was not until a quantitative value was placed on thyroxin that the real physiologic processes involved could be demonstrated. It seems that one of the most important results of this work has been the furnishing of the material with which quantitative values could be determined.

The moment we know that in a myxedematous patient the administration of 10 mg. of thyroxin increases the basal metabolic rate 30 per cent, we have the key to the explanation of the relief of a very complex clinical syndrome. The edema is relieved. The sluggish mentality is relieved. The dry scaly skin becomes moist. The hair ceases to fall out and becomes soft. The voice that has been very slow, returns to its normal tone and character. The mentality which has been befogged becomes clear, and the individual expresses his normal personality. In short, every cell in the body responds with its own expression of activity. It seems impossible that all this can be done with a single crystalline substance, and because our knowledge has been limited as to just what and how much was going on, we have let visible changes lead away into theories that are narrow and which obscure rather than enlighten. But, when we know that simultaneously with the clinical improvement the basal metabolic rate has been increased 30 per cent, it follows axiomatically, from laws of mechanics, hydraulics, and physics, that very fundamental changes have occurred throughout the entire body. It has long been known that the thyroid influences basal metabolic rate in the body. It is a present-day conception that it is through metabolic processes that the thyroid produces its physiologic effect, but the scope of this action and the chemical processes involved have not been emphasized or established.

In order to explain the action of thyroxin, when 10 milligrams of the substance increases the metabolic rate 30 per cent, as Plummer puts it, it would take a discussion as broad as biology itself. This aspect of the question must receive greater attention in order to bring out the physiologic processes involved in the function of the thyroid, and with it the other ductless glands. The scope of the problem is so broad that several investigators viewing it from entirely different standpoints can each obtain results satisfactorily conforming to their conclusions, but no one of which forms a fundamental physiologic process. For instance, investigating the question of resistance to infection, the removal of the thyroid establishes the fact that in thyroidless animals infection is much more prevalent. This is of interest to the bacteriologist, serol-

ogist, immunologist, etc. The fact that the growth of bones is retarded is an entirely different phase of the subject, and so a long list of investigations concerning the thyroid which have been carried on with positive results leading to various conclusions concerning its activity could be cited.

Until it was shown that the confusing clinical syndrome found in myxedema could be entirely relieved by a single substance, the problem as to how many active constituents occurred in the thyroid could not be settled. In fact, the fundamental reaction underlying all expressions of thyroid activity could not be made as long as clinical symptoms alone were used as a criterion of physiologic activity. But, establishing the relation of thyroxin to the basal rate of metabolism in mathematical exactness furnishes the first clew to the physiologic processes involved and it is evident that physiologic response to an injection of thyroxin is found in a summation of the activity of all the cells in the body. If anyone chooses to investigate any one particular process he will find that process altered, for a change in metabolic rate is accompanied by fundamental changes in every aspect of the reactions going on within the body. This is where the application of physics, mechanics, hydraulics and chemistry must be made in order that not only the changes produced by the administration of thyroxin, but what the effect of a second factor would be, may be understood.

The injection of adrenalin into an animal with a normal basal metabolic rate will necessarily be different from the injection of adrenalin into an animal with a metabolic rate 30 per cent above normal, if viewed purely from a consideration of the physics involved. As Plummer has pointed out, it is possible to explain the supposed relation between thyroid and adrenalin on grounds involving the rate of flow of the blood, entirely apart from any other action.

When it comes to establishing relations between the other ductless glands and the thyroid, progress can only be made when the various activities of the glands are viewed in as broad an aspect as Plummer has suggested for the action of thyroxin. Disturbances of the pituitary lead to changes in basal metabolic rate which are marked but are less than those found in thyroid disturbances. Changes in the pancreas and what we know of the adrenal also lead to changes which are smaller than that produced by thyroxin. We can at least tentatively assign to the thyroid the supplying of an agent which is of fundamental importance in the production of energy. This can be carried one step further

in a chemical sense, and we may assume that thyroxin is involved in the production of carbon dioxide. The other ductless glands then assume positions of secondary importance to the thyroid, in carrying out these chemical reactions, and may be assigned the rôle of preparing the various metabolites for their final action with thyroxin. No definite hypothesis can at this time be given beyond the fact that the various clinical syndromes produced by hyper- or hypo-action of the various glands, are syndromes resulting from the effects of these substances throughout all the cells of the body, through their action in maintaining the rate of energy production going on within the cells.

It is perfectly possible to explain the apparent selective action of various internal secretions to restricted portions of the body on these grounds, and in fact selective action vanishes when the action of the gland is placed on this broader basis.

Besides the action suggested for certain of the ductless glands of preparing metabolites for their final interaction with thyroxin with the production of energy, we must also assign to some agents within the body the task of taking care of bi-products and of elaborating other substances. Nitrogen compounds include toxic substances among their number. For the proper elaboration of these compounds, which assume fundamental importance in normal physiology, some very substantial mechanism must exist. That certain of the ductless glands should be given the power to affect the rate at which the body can prepare and care for nitrogenous compounds seems highly probable, and of late the parathyroid assumes great importance as one of the glands thus involved. That other glands are concerned seems also to be indicated.

It was therefore of great interest to determine the chemical nature of this iodine containing compound which occurs in the thyroid and is so fundamentally involved in normal physiology. Analysis has shown that it contains an indol group with the iodine undoubtedly attached to the benzene ring, and that on the carbon atom adjacent to the imino group of the indol ring there is an oxygen atom (Fig. 164). For reasons given hereinafter, it appeared desirable to emphasize the presence of the oxy-indol nucleus and it appeared equally desirable not to emphasize the presence of iodine. The substance was therefore named "Thyro-oxy-indol," which has been shortened to "thyroxin" for every-day reference to the substance. At first we attempted to show that the activity of thyroxin was due to the oxygen condensing with the amino group of an amino acid and the carboxyl group of the amino acid reacting with

occurring within the animal organism. Are these substances also concerned in the maintenance of the basal metabolic rate?

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## CANCER OF THE THYROID GLAND\*

D. C. BALFOUR

It is, I believe, the common opinion of clinicians and surgeons that cancer of the thyroid, at least if it has progressed to a stage in which the clinical diagnosis is certain, is incurable. When early malignancy is discovered during the course of operation, this pessimistic attitude is not mitigated even by a radical extirpation of the entire gland. Whether such an attitude is justified by the results obtained in the routine employment of the most advanced clinical, pathologic, and surgical methods, is open to some doubt; it is my purpose in this investigation to determine the facts.

The frequency of cancer of the thyroid, as compared with benign enlargement of the thyroid, can only be estimated, since an unknown and probably a relatively small percentage of the so-called "simple" goiter group of patients seek medical or surgical advice. Of 6359 cases of goiter, exclusive of the exophthalmic group, seen in the Mayo Clinic during the six years from January, 1910, to January, 1916,† we have classified 103 cases as cancer, a percentage of 1.6. The cancer incidence, based on all patients with goiters (14,456), coming to the clinic from Jan. 1, 1910, to Aug. 1, 1918, is 1.19 per cent. The age incidence in the 103 cases is:

8 cases ( 7.9 per cent) between twenty and thirty  
10 cases ( 9.6 per cent) between thirty and forty  
30 cases (29.1 per cent) between forty and fifty  
30 cases (29.1 per cent) between fifty and sixty  
25 cases (23.3 per cent) more than sixty

Eighty-one and five-tenths per cent of the 103 patients were more than forty years. Sixty-eight (65 per cent) of the patients were females, 35 (35 per cent) were males.

In reviewing this series from the standpoint of etiology, the most impressive fact is that in almost every cancer of the thyroid we have

\* Reprinted from Med. Rec., 1918, xciv, 846-850.

† This period was chosen in order to give a fair indication of the results of operation, and to furnish a basis for prognostication as to ultimate results.



seen in the clinic there has been a history of a long preëxisting goiter. In the very few instances in which we have been unable to obtain a history it is quite probable that small adenomas existed within the gland, the presence of which were not known to the patient. In our own experience we have not met with a single instance of cancer of the thyroid which gave unmistakable evidence of having developed within a normal gland. This fact parallels the low primary cancer incidence in other ductless glands—the thymus, pituitary, adrenal, the spleen, etc. The significance of this point, that is, the marked difference in tendency toward malignant degeneration possessed by the normal thyroid and the thyroid in which benign tumors (cysts and adenomas) have developed is, that such tumors can be justly considered as points of chronic irritation in an otherwise normal organ.

Langhans stated that cancer of the thyroid originates from unutilized embryonic tissue, and that such tissue remains quiescent until the necessary factor of irritation is introduced, which may be and usually is adenomatous. A further factor of interest in the agency of irritation is that of external trauma. Although patients with small goiters frequently erroneously attribute various sensations in the neck to a direct blow, we have not seen any evidence that malignant change has been occasioned by injury to the gland. However, there have been observed in the clinic 7 cases in which malignancy occurred in an enlarged thyroid that had previously been "treated" by injections of various irritants and by the application of "absorbents." Such cases are even more convincing examples of the fact that chronic irritation is the chief factor in inducing malignant changes, and should be the final argument against useless and dangerous methods of treatment. As pointed out by Plummer, the disease has never, in our experience, developed in a distinctively and purely hyperplastic gland.

The clinical diagnosis of cancer of the thyroid is relatively simple when the process is advanced, but it is impossible when the malignancy is in the early stage. The diagnosis of malignancy, before it can be recognized as such by palpation, can only be based on the rate of growth. Malignancy must always be considered when a history is obtained of rapid growth of a goiter that has been more or less stationary in size. In well-developed cases, the board-like resistance and the fixity of the gland are sufficient to justify a diagnosis of malignancy, if the history and Wassermann test have excluded the rarer conditions of hemorrhagic acute thyroiditis and syphilis. Moreover, when the disease has become

recognizable by palpation, symptoms and signs of pressure, either tracheal or esophageal, are usually present. Rarely, hoarseness and dysphagia may be early in evidence, and, in the absence of other symptoms, may be suggestive.

The relative frequency of thyroid malignancy in which there is an absence of signs or subjective symptoms, is well shown in this series of cases. In only 18 per cent could a positive clinical diagnosis of cancer be made. In 36 per cent, malignancy was considered as a possibility in the preoperative diagnosis, while in 46 per cent the condition was not even suspected until it was discovered during the course of operation or later by pathologic examination. It should be stated that the latter figure (46 per cent), although it represents the number of cases of cancer of the thyroid in which no note was made of such a possibility, could be lowered if in the large group of hard, firm adenomas which we see in the clinic the possibility of malignancy should be regularly noted. In doing this, however, the total percentage of accuracy in diagnosis would be considerably lowered, because of the small percentage of such adenomas that are malignant, and as surgical treatment is clearly advisable in the entire group, the discussion as to the question of malignant change is not only merely of academic interest, but dangerous in its tendency to delay.

It is, of course, true that not infrequently malignancy has been clinically suspected although no evidence of it was found at operation. This is chiefly explained (1) by the fact that certain changes simulating malignant degeneration occasionally take place in an enlarged thyroid (the most confusing cases are low-lying adenomas in which there has been a considerable deposition of lime salts), and (2) because the clinician, being aware that this large percentage (46) of malignant cases found at operation shows insufficient evidence to support even a provisional diagnosis of malignancy, accepts the chance of an error in the hope of exhibiting diagnostic acumen.

These figures are most eloquent testimony of the difficulty of diagnosis of early carcinoma of the thyroid; in no other region of the body is beginning malignancy so well concealed. The explanation of this fact is found in the close analogy between benign nodules and malignant masses, as in both there is a marked tendency for the masses to remain covered by healthy thyroid tissue and not to reach the thyroid capsule until each has attained considerable size. This similarity should be stressed for it means that the signs of malignancy are not noticeable

until the process has been in existence for some time, and for this reason a strong argument is added for early operative interference in cases of nodular goiter. It means, too, that only by such interference will the cancer incidence in the thyroid be lowered. Just as in other conditions that are either definitely precancerous or provocative of cancer, such as chronic gastric ulcer, gall stones, and cervical erosions, it is criminal to agree to delay operation in the belief that malignant changes can be recognized in time, so in cases of nodular goiters, waiting for evidence of malignancy is even more inexcusable, and is fatal to the best interests of the patient.

The difficulties of diagnosis, moreover, are not wholly concerned with the clinical manifestations of the disease. Carcinoma of the thyroid gland may be of such a broken-down character, particularly when the malignancy has developed within a cyst, that it is occasionally difficult, either at operation or by pathologic examination, to differentiate benign and malignant necrosis.\*

An atypical microscopic picture is responsible for the fact that in several instances a surgical diagnosis of malignant goiter has been made at operation without a confirmation by the pathologist. It is of importance to note that in some of these cases, although the surgical opinion remained unsupported after repeated pathologic examinations, the later developments proved that the surgical diagnosis was correct. It is advisable, therefore, in such cases, to recognize the relative value of the surgical record, and of the pathologic report. A discrepancy between the surgical record and the pathologic report is most likely to occur in those cases in which the malignancy is of very low grade activity, and in which the pathologic picture is that of simple goiter.

Diagnostic difficulties at operation are also found in those cases in which muscles and thyroid capsules are adherent, due to the inflammatory changes that have followed injections, or other local treatment. The diagnosis, however, in this group can usually be made at the operating table from the fact that if the condition is benign, the indications of malignancy become less with further exposure of the gland, while in cancer the reverse is true.

Errors in diagnosis have also occurred because of the fact that a

\* Dr. L. B. Wilson, when he left for active service in France in February, was independently preparing a complete study from a pathologic standpoint of the malignant thyroid tumors.

malignant process may develop in close relationship to but quite independent of an enlarged thyroid. The following case will illustrate:

The patient, Mrs. J. O. A. (Case 82318), had an adenoma the size of a large grape-fruit in the right lobe. Following the enucleation of this adenoma I found a mass the size of a small lemon crowded up in the right submaxillary triangle. It was hard and adherent to the surrounding structures and at first was thought to be a malignant superior pole of the right lobe. Further investigation, however, proved it to be a carotid body tumor, which necessitated an extensive dissection for its removal.

Rarely have the clinician, the surgeon, and the pathologist all erred in pronouncing a given case to be malignancy of the thyroid when the future course of the condition proved the error in the diagnosis. This occurred, however, in one case in the present series. The patient exhibited a hard infiltration of the entire gland with a history of rapid enlargement and marked tracheal pressure. A clinical diagnosis of probable carcinoma was made and at operation the condition was thought to be malignant and the tumor irremovable. A section for microscopic examination was pronounced carcinoma. The patient seven years later is in good health with no marked enlargement of the gland. In all probability this was a case of thyroiditis of the "woody" type described by Riedel.\* The thyroid gland being unique in its power to develop hyperplasia of its cellular elements, in certain types of infections, occasionally simulates very closely a malignant degeneration.

In considering the indications for operation and the surgical problems to be met in the operative treatment of malignant thyroid tumors, it may first be stated that when the clinical diagnosis is positive, surgical interference should be advocated only under exceptional circumstances. In our own experience, at least, infiltrating, diffuse, advanced cancer of the thyroid, when the capsule has been perforated and muscles and glands involved, has never been cured even by the most radical methods, and such methods are attended by a prohibitive risk. Under such conditions, therefore, the only purpose of surgery would be the relief by tracheotomy of tracheal pressure with actual or impending suffocation, and even this procedure may be one of considerable technical difficulty, great risk, and dubious results. As a rule, therefore, it is much better to advise the use of radium, x-ray exposures, and whatever other palliative measures there are available.

Even when the malignant process is less extensive, and the anterior

\* Riedel: Quoted by Crotti, A.: Thyroid and thymus. Phila., Lea, 1918, 109.

and lateral relationships of the gland make it appear possible and reasonably safe to remove the entire gland, it is important to remember that there is a liability to encroachment of the disease on the trachea, the esophagus, or both. This complication may vary between actual invasion of these structures and firm attachment to them without invasion. In the first complication the possibility of obtaining a cure is rendered very unlikely although we have had one case in which the lateral wall of both the trachea and the esophagus was excised with the thyroid; the patient is alive and well seven years afterwards. In the second complication, the malignant mass may be crowded between the trachea and the esophagus, so that in the traction necessary to expose this portion of the tumor, the esophagus may be dragged out of its bed and injured before being recognized. An esophageal fistula is, therefore, one of the possible secondary complications, and has occurred after the removal of a malignant thyroid.

The more frequent and more urgent surgical problem concerns the trachea. When there is marked tracheal obstruction prior to operation in a malignant thyroid, the tracheal rings, even if not invaded by the disease, are oftentimes so softened that tracheal collapse may occur at a most inopportune moment and with comparatively little provocation. As C. H. Mayo early pointed out, the trachea in malignant goiter is more apt to flatten itself in an anteroposterior direction, than to develop the scabbard trachea which is seen in benign and bilateral enlargements of the gland (Figs. 166 and 167). Therefore, when there is evidence of tracheal pressure, especially if malignancy is suspected, any measure should be made use of that will minimize the technical difficulties and the risk of operation. Among such measures the most important is local anesthesia.

Since tracheotomy is not an unusual emergency operation in malignancy of the thyroid, the surgeon, who has acquired the ability, by practice in surgery of nontoxic goiter, of quickly isolating the trachea as the first step after the surface of the gland has been exposed, is in an advantageous position when such an emergency arises. In some cases the necessity for tracheotomy may occur while the patient is being prepared for operation; it may occur at any time during the course of the operation, or, more rarely, during the post-operative period, even though the gland has been entirely removed.

Tracheal obstruction, after total or subtotal thyroidectomy, may be owing to one or all of the following causes and conditions; (1) Injury during operation to the nerve supply of the laryngeal muscles; (2)

lary edema of the tracheal mucous membrane; (3) secondary tomas, and (4) softened tracheal rings. As a measure of safety,

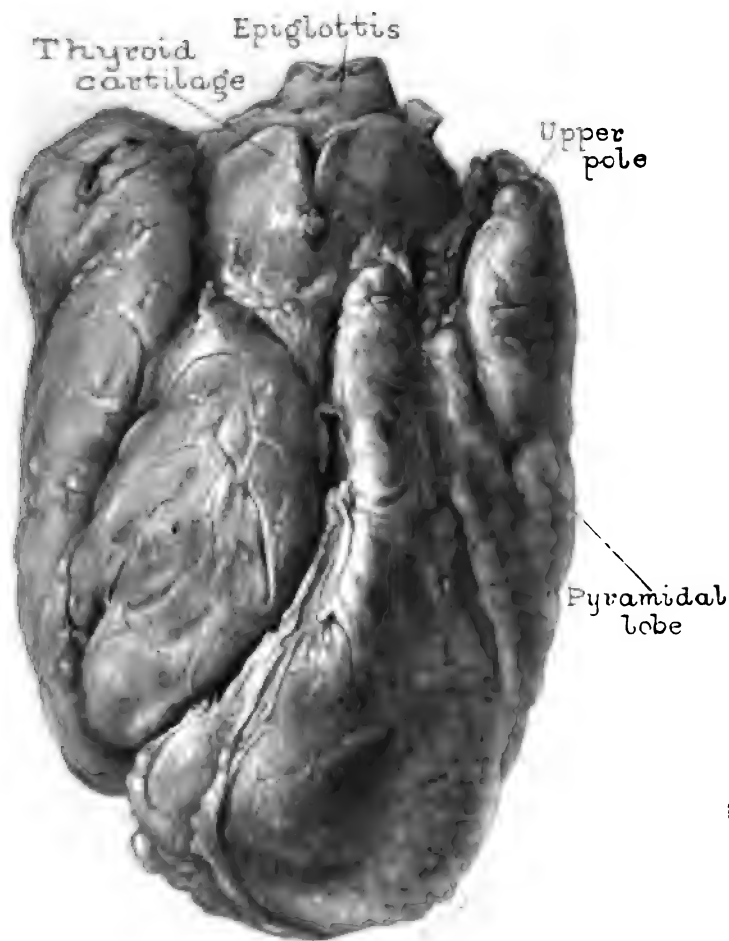


Fig. 106.—Anterior view of enlarged thyroid gland.

following operation for malignant thyroid, it is wise to have in the patient's room the equipment necessary to perform an immediate aseptic tracheotomy.

In this connection it is of interest that the possibility of secondary tracheal obstruction is not restricted to malignant conditions. I have

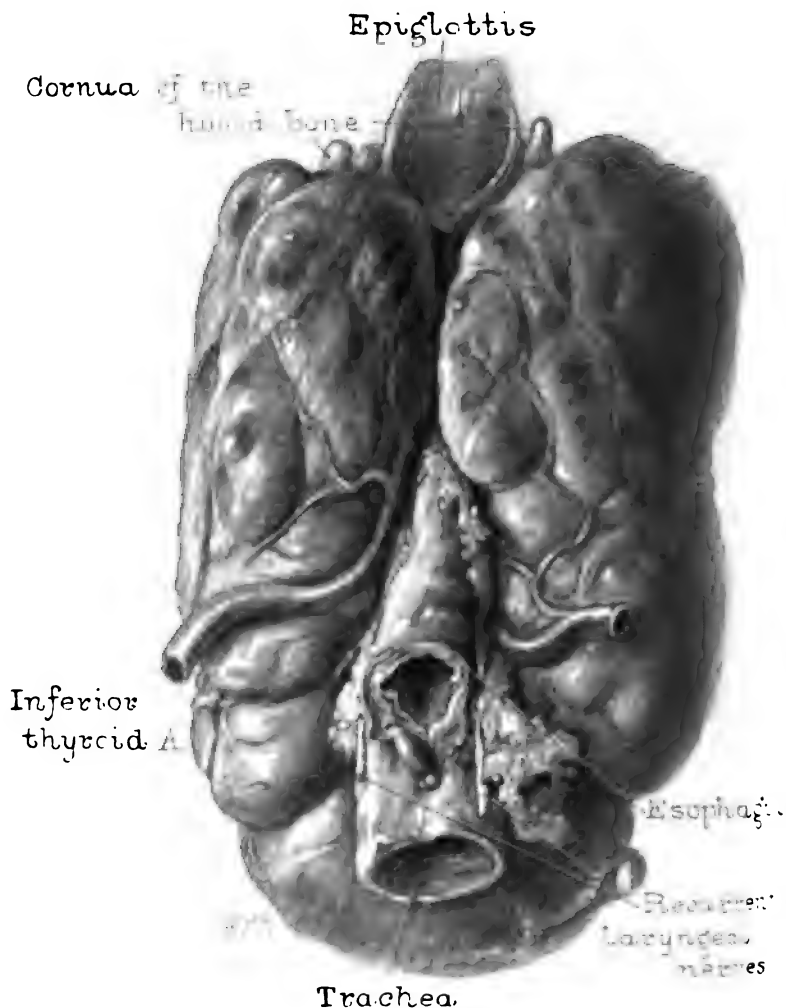


Fig. 167.—Posterior view of thyroid gland surrounding trachea and esophagus.

had one such case occurring in a non-toxic goiter. There had been nothing unusual in the operation except that it was necessary to remove

a large amount of thyroid tissue, as the enlargement was due to multiple degenerating adenomas, which had extensively involved both lobes. After enucleating the tissue from all the diseased areas of the two lobes by the double resection method, comparatively thin shells of thyroid tissue remained. Further, along with the treatment of the lateral lobes, the removal of a large pyramidal lobe, which had wrapped itself around the upper rings of the trachea, necessitated a rather extensive stripping of the trachea. Nothing occurred during the course of the operation to give warning of the immediate or late complications, but the following day the patient complained of difficulty in breathing, which gradually increased; the breathing became crowing in character, and, thirty hours after the operation, it was necessary to do a tracheotomy. It was a surprise to find no visible cause for the obstruction, as the operative field was in perfect condition. The tracheotomy tube was left in place for forty-eight hours, and its removal did not cause any recurrence of the difficulty. The complication in such a case was probably the result of an edema of the mucous membrane brought about by the close dissection of a large surface of the trachea.

Total thyroidectomy must, of course, be followed by the administration of thyroid substance. The recent studies of Plummer, which establish the exact relationship between thyroid activity and metabolism, for the first time have made it possible to determine with absolute accuracy the amount of the active principle of the thyroid necessary to maintain normal metabolism in such cases. Since this is possible, and since Kendall has been able to isolate and synthetically to produce the active principle in thyroxin, any objection to total thyroidectomy in malignancy of the gland on the score of post-operative disturbance in metabolism is practically eliminated.

In those cases in which malignancy has not been suspected, but is discovered at operation within the substance of an adenoma, the question of total extirpation of the gland must be determined at the time. In reviewing the results in such cases it has been interesting to find that total thyroidectomy was rarely performed under such circumstances, and the indications are that radical extirpation is unnecessary.

Before discussing the results of operation in malignant cases, it is well to consider the question of the danger of malignant change taking place after operation for simple goiter. The fact that occasionally patients who have been operated on for a simple goiter have later developed malignancy in the remaining portion of the gland, raises two



questions, first, whether malignancy has been overlooked, and, second, whether real cancer-prophylactic value is secured in operating in simple goiter.

The first possibility of overlooking a malignant process in the portion of gland remaining cannot be denied. This apparently occurred in one patient in the series, from whom a lobe had been removed, and who returned to the clinic in about six months with malignancy well developed in the opposite lobe. We believe, however, that with the present methods of conducting operations in simple goiter, the risk of such malignant development is a negligible factor. In 90 per cent of operations at the clinic for simple goiter, a double resection which insured thorough exploration of both lobes for adenomatous masses, both small and large, is done. With such a principle carried out as a routine procedure, the danger of leaving adenomas that might attain further growth, either benign or malignant, is reduced to a minimum. Inasmuch as cancer in the thyroid almost invariably develops from within outward, as pointed out by Kocher, this exploration of the interior of the gland is of the greatest importance in making possible the early detection and removal of cancerous or precancerous adenomas.

The further question as to the assurance which can be given a patient in regard to the danger of malignant change taking place in the thyroid after the operation, can be answered by saying that, although such assurance cannot be absolute, it can be practically so. An incontrovertible argument for operation in cases of adenomatous goiter is the fact that cancer is practically not known to have developed in a healthy thyroid gland. Preëxisting disease has always been in evidence, so that adenomatous goiter may be looked on, to a certain extent, as a precancerous condition. It is to be hoped, therefore, that adenomatous goiters in the future will not be permitted to develop malignant changes, but that surgical assistance will be sought opportunely and, with the correction of the deformity, the catastrophe of malignancy be obviated.

In considering the results, the investigation of which was my primary object in writing this paper, it was found that of the 103 cases of cancer of the thyroid seen in our clinic, 63 patients have come to operation. The remainder, constituting 38 per cent of the number in which there was a positive pre-operative diagnosis of cancer, have been put on x-ray or radium treatment.

Definite information regarding 42 of the 63 patients was secured.\*

\* This data was secured during 1917-1918.

Four of the patients operated on died while under our observation. Twenty of those who survived the operation are now dead, all apparently of the disease. They lived from a few weeks to four and one-half years. Of the remaining 22 patients, the information is positive in five instances of extensive recurrence, and a probable early death. In 17, however, there is freedom from any evidence of recurrence, and the patients are in good health. In 3 of these the operation had been done less than one year, in 3 between one and two years, in 4 between two and three years, in 1 between three and four years, in 5 between four and five years, and in 1 more than five years. To recapitulate, 6+ per cent is the operative mortality; 47.6 per cent died soon from recurrence; 11 per cent have recurrence; total 65.6 per cent deaths or probable early death from the disease.

Thirty-five per cent show no evidence of recurrence in from one to five years, but this percentage cannot be taken as representing the actual ultimate results because of the short time which has elapsed since some of the patients have been operated on and of the fact that in cancer of the thyroid unusually late recurrences are not rare. Only 14.6 per cent of patients with diffuse carcinoma are alive without recurrence. Of the cases of carcinoma within an adenoma, without gross or microscopic evidence of malignancy in the gland-tissue outside the wall of the adenoma, 69 per cent of the patients are alive without recurrence. A study of these results in the series of cases, and of the individual case gives us valuable information as to what can be accomplished in the surgical treatment of cancer of the thyroid:

1. The most important lesson is presented in the fact that in 46 per cent of the cases of cancer of the thyroid, no clinical manifestations of the disease were in evidence. This group shows by far the highest percentage (about 70) of patients free from recurrence at the present time. In other words, the great majority of apparent cures have occurred in those cases in which the malignant change was an unexpected finding. Total thyroidectomy was rarely performed in this group. In most instances the lobe containing the tumor and the malignant process was removed, but in many the enucleation of an adenoma was the procedure.

2. In any nodular goiter suddenly exhibiting an increased rapidity of growth, immediate surgical treatment should be urged.

3. When clinical evidences of cancer are present, the results of surgical treatment are discouraging. Total extirpation of the gland

appears to be indicated only when both lobes are grossly involved the disease, and when past experience warrants surgical interference the particular case.

4. Recognizable involvement of cervical glands usually means the time for surgical cure is past. Occasionally, however, just as the unexpected occurs in the treatment of extensive cancer elsewhere, a apparent cure is obtained. In 1913, I removed from a patient (Case 81854) the right lobe of the thyroid containing a malignant adenoma. A mass of glands in the submaxillary region was also proved to be carcinomatous. A week later a block dissection was done. The patient is now alive and well with no evidence whatever of recurrence. Such cases are, however, notable exceptions to the rule.

5. Gross involvement of trachea or esophagus is almost a certain sign against curability, and yet one may be tempted into an extensive and dangerous operation to remove the diseased tissue because of the knowledge of an unexpected result in the past. A patient (Case 73733) was operated on (by E. S. Judd in 1912) for a malignancy of the left lobe which was found to involve the lateral walls of both trachea and esophagus. The involved areas were both excised, with primary closure, and although bougies were required later to maintain the caliber of the esophagus, the patient is now, six years after operation, in perfect health and has no local disability.

6. The last and most important lesson learned from the standpoint of prophylaxis, is the fact that in this series the average number of years of abnormal growth in the thyroid preceding the operation was 11.6. This is proof positive of the advisability of the early removal of well-developed thyroid nodules, and it is a regrettable fact that not infrequently we meet with cases of hopeless thyroid cancers in which a tumor has been present for many years, but the patient had been able to secure the advice of "leave it alone, it will never bother you."

Finally, the treatment of cancer of the thyroid should be that of the treatment of precancerous lesions elsewhere, that is, prompt surgical treatment of the precancerous condition in the thyroid—the adenoma.

# THE PRINCIPLES OF THYROID SURGERY\*

C. H. MAYO

Goiter has received medical and surgical attention, as annals of medicine make record, from time immemorial. Because of its conspicuous location, diseases of the thyroid are far more noticeable than those of other duct-bearing or ductless glands, and yet most of the knowledge concerning it has been acquired within the last fifty years. The chronic character or cyclic recurrence of some diseases of the thyroid is evidenced by the remarkable number of remedies, supposed to be exceedingly effectual, which have been used in their treatment; surgery was employed only as a last resort. Because of the high mortality—most operations were done only when necessitated by obstruction to respiration or circulation. A surgical vicious circle ensued; a high mortality led to late operation, and late operation to a high mortality. The seriousness and frequency of infection was also a great factor in retarding surgery, and progress was not made until the period of antiseptics and asepsis, which developed methods of safety and advanced all surgical knowledge.

The thyroid has a single anlage developing between the portions of the tongue, which very rarely remains in this location. We have seen but three such in 12,000 goiter patients operated on, and in several thousand more unoperated patients with goiter. Midline cysts of the neck are occasionally seen in the hyoid region, incident to defects in development, and are usually connected with a small remnant of the gland behind the hyoid. The pyramidal lobe, occurring in a considerable percentage of persons, is the result of a stringing out of the gland through the attachment of the central portion to the hyoid in its descent.

Due to the care with which nature has guarded its blood supply, the thyroid, weighing approximately but an ounce, is a gland the secretion of which is of the utmost importance; this we see proved in the vege-

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tative type of animal existence which occurs in cretins who are without this gland, or those who subsequently lose it—the myxomatous. No other gland in the body has been so well cared for in circulation by nature as the thyroid, all of the blood in the body passes through it once an hour. With its four regular arteries supplied by various main trunks, and the anomalies leading to greater circulation nothing should interfere with it. The gland consists of a mass of alveoli or vesicles lined with a single layer of columnar cells. Having no duct it has been assumed that its secretion passes through the lymphatics and through the venous system as a hormone. There is no outlet from the interior of the vesicles, and the secretion of colloid accumulates here. As has been previously stated, it is evidently true that these cells deliver a secretion from their bases, and accumulations within the vesicles should they ever leave them, are passed back through the cells as a filter.

Our surgery of the thyroid was developed for the removal of goiters causing pressure which interfered with respiration or the circulation in cases of great deformity. These goiters consisted of colloid adenomas, cysts and fibrocystic, malignant or tuberculous tumors. Another variety of disease, exophthalmic goiter, with its various pseudonyms, was recognized as probably being associated with a diseased thyroid because in it the gland was palpably changed from the normal. The mortality in operations on the gland in this condition was so high that even masters of surgery, such as Kocher, for a long time did not consider it amenable to surgery. Yet the foundation of our present knowledge of the thyroid is built on a study of the overworking or hyperplastic thyroid, the normal gland and the hypofunctionating gland of myxedema dropping into their respective relationships after these discoveries were made. The thyroid undoubtedly is one of the most important glands in the body, and while we are far from a complete knowledge of its activities, the work of Plummer and Kendall, through investigation into the physiologic action of its secretion, is such as to bring us to the verge of a realization of its fundamental effect on life. Iodin was discovered in 1812 by B. Courtois. Baumann,<sup>1</sup> in 1895, found iodine to be associated with the thyroid secretion, and Kendall,<sup>2</sup> in 1915, separated, as a pure crystalline substance, the organic compound which contains the iodine.

Kendall has been able to separate the compound of the thyroid containing iodine from the balance of the gland. This is accomplished by

destroying the proteins of the thyroid by means of boiling with a strong alkali, which does not decompose the iodine-containing compound, and, by suitable treatment, it can be separated as a pure crystalline substance containing 65 per cent of iodine, its formula being  $C_{11}H_{10}O_3NI_3$ . The compound contains an organic nucleus called indol, as well as oxygen. Wishing to emphasize these two facts and to relate it to its sources, Kendall called the compound thyro-oxy-indol, which has been abbreviated to thyroxine. Its function is involved in the most fundamental processes of life, that is, the production of energy. Kendall's work has furnished the only pure crystalline compound ever separated from the thyroid that possesses the same physiologic activity as the gland itself. This work places the investigation of the thyroid on a clear chemical basis and has made it possible to study quantitatively the action of the thyroid hormone.

Plummer, in the observation of many thousands of cases of goiter, numerous cases of cretins and of myxedematous patients, has shown that the rate at which energy is produced by the animal organism is controlled by the amount of thyroxine which is acting within the cells of that body. While not the only factor influencing the rate at which we live, it probably has more to do than any other substance with the governing of the speed at which energy is produced in the body. Plummer shows the average basal metabolic rate of exophthalmic goiter patients at the time of coming under observation to be 57 per cent above normal, and the average rate in those in whom ligations were done and who returned in three months, to be plus 39 per cent. The average rate eighteen days after thyroidectomy is plus 19. Ligation probably causes the metabolic rate to drop approximately 15 per cent. Patients having adenomas of the thyroid also show variations in the output of the gland, the average rate on coming under observation being plus 39, and the average rate eighteen days after thyroidectomy slightly above normal. The average energy transformation for normal persons is approximately 39 calories to a square meter of body surface an hour. The basal metabolic rate of normal persons does not fluctuate more than 10 per cent above or below this average. Plummer's observations show that the thyroid hormone (thyroxine) determines the rate of formation of a quantum of potential energy available for transformation on excitation of the cell. The total amount of thyroxine in the tissues of the body of normal persons is in all probability approximately 13 mg. Each increase of 0.033 mg. (approximate) of the thyroxine in the tissues of the

body increases the rate of energy output 1 per cent. Other factors being constant, the total energy output of the body varies with the amount of thyroxin in the tissues and the rate of excitation.

The work of Plummer is of the utmost importance in showing the thyroid to be a most active factor in the metabolism of the individual. The metabolic rate is raised or lowered by the activity or nonactivity of the thyroid and is measured by the amount of oxygen utilized from the air in respiration and the output of carbon dioxide in the expired air.

Exophthalmic goiter or gland hyperplasia, and overactivity develop an enormous increase in the metabolic rate, running in cycles of recurrence above the basal metabolism from 16 to 100 per cent or more according to the severity of the case. We thus have small exophthalmic goiters which are often more active in their effect than others which are evidently several times larger than normal. There is little or no deposit of colloid, as a rule, in the active cases, the colloid serving as a suspension agent for secretion, being deposited in the interior of vesicles when seen in simple goiters and as occasionally seen in areas of exophthalmic goiter. Therefore, we see that the energy output of the gland may vary greatly and the development of the remaining lobe, or even of half a lobe, after operation or partial thyroidectomy may subsequently cause a metabolic rate of from 40 to 90 per cent above normal; this, however, rarely happens. It is difficult in some cases to tell the exact amount of gland it is necessary to remove in order to secure a drop in metabolism to nearly normal limits. Thus in a few cases a second, and in a still smaller number a third operation is required. They are not the result of the failure of surgery to cure exophthalmic goiter, but are a still greater proof of the value of surgery in its cure. The removal of a larger portion of the gland accomplishes a cure depending on the activity of the individual gland, as the benefit of the operation is obtained through the reduction of secretion. Thyroid secretion will persist in the body for approximately eighteen days (Plummer). We are still lacking in the knowledge of the activating agent which causes hyperplasia, the discovery of which is undoubtedly impending.

The simple goiters of adolescence are common. Only such of them require operation as are troublesome because of pressure or are unsightly and resist treatment. In some persons they are associated with a demand of the body for thyroxin, and iodine in most any form relieves the gland of its colloid. The gland is not hyperplastic. In persons under twenty-five years of age small adenomas in the thyroid and the simple colloid

goiters are only occasionally recommended for surgery. Later in life the degenerations which occur in goiters of long standing, such as encapsulated adenomas and encapsulated colloid areas, when the secretion has become reduced, may develop thyrotoxic conditions. Kocher pointed out the fact that the degenerations often occur in women from forty to sixty years of age, whose goiters of long standing are altered by iodine treatment. The older the person when goiter develops, the more quickly must degeneration occur. These patients have staring, but not protruding, eyes, widening of the fissure through sagging of the lower lid, and, because of the rapid pulse and tremor, the condition is often looked on as exophthalmic goiter. Plummer has pointed out the distinction between this condition and exophthalmic goiter.

Simple types of goiter or adenomas often grow to enormous size and occasionally may project into the chest, as substernal goiters. In some instances the entire thyroid enlargement is beneath the sternum, and the troubles occurring are due to degeneration or pressure, with great increase in the size of the veins of the neck and chest, showing the impeded return circulation. The radiogram is an important factor in disclosing the size and location of such tumors.

The dangers incident to the operation are the condition of the patient, as in exophthalmic and thyrotoxic goiters, and those due strictly to the operation, as loss of blood, secondary hemorrhage, interference with respiration, injury to the recurrent nerves and to the parathyroids. The parathyroids and the recurrent nerve should be guarded in simple goiter by leaving the posterior part of each lobe of the gland on the posterior capsule, and by care in the use of forceps, and care in suturing the remainder of the gland and in the ligation of its vessels. Laryngoscopic examination should be made before operation to disclose the condition of the vocal cords, as partial or complete paralysis of an abductor or adductor may be present with but little change in the voice, and especially as unilateral tumors on the right side may produce paralysis of the left recurrent nerves, and surgical injury to the right side may result in total loss of voice. The parathyroids controlling the nitrogen elimination should be preserved as a guard against tetany. Local anesthesia may be used in special cases, but ether and local anesthesia are used in most instances.

The best method of approach is through a low collar incision. The sternothyroid and sternohyoid muscles should be cut high and resutured if they interfere with the surgical exposure of the gland; greater expe-



rience seldom requires their division. The isthmus should be removed and double resection is the operation of choice in simple goiter, while in the exophthalmic type, removal of the larger lobe, isthmus and part of the remaining lobe is the most common procedure. Drainage is instituted for twenty-four hours in the majority of cases, although in substernal goiter, the cavity of which does not immediately become obliterated by intrathoracic pressure, should not be drained longer than a few hours at most, to retain a blood clot for organization; otherwise drainage in such cavities is indefinite.

#### RECURRENCE OF GOITER

In the simple forms of goiter, the same condition may remain in the portion of the gland preserved, to develop occasionally a recurrence of similar growth. Waves of activity of the gland occur and a small gland occasionally creates a far greater effect than a large one, through variations in its secretion, the quantity of the output or the resistance of the individual. Failure properly to estimate this activity is inevitable in a small proportion of cases. The cures by operation, however, are practically 70 per cent, with many of the remaining cases improved. Plummer explains to us many questions of recurrence, formerly supposed by medical men to indicate that surgery was not warranted. The results obtained by operation approximate what should be expected from the work of Plummer and Kendall, which I consider at this time the most important advance made in medicine of the chemistry of life.

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## SPLENECTOMY FOLLOWING RADIUM TREATMENT FOR MYELOCYTIC LEUKEMIA\*

H. Z. GIFFIN

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The first case of splenectomy for myelocytic leukemia was reported in 1866 by Bryant. His patient was in poor general condition and the spleen was very large; death occurred two and one-half hours after the operation. Bryant reported a second fatal case in 1867. The spleen in this instance was again very large and the general condition of the patient poor. Death occurred immediately after the operation.

The history of splenectomy for myelocytic leukemia is a repetition of the history of Bryant's cases and is extremely tragic. From 1866 to 1900 the operation was not infrequently performed. Approximately 86 per cent of the patients on record died within a few hours of the operation. The patients for the most part were weak, toxic, and anemic, with huge spleens and high leukocyte counts, and had insufficient vitality to respond favorably when surgical treatment could be suggested and accepted. It is true that they were operated on at a time when least could be expected. The experience of various surgeons was similar and the conclusion naturally followed that splenectomy for myelocytic leukemia was in no sense a justifiable operation.

Bessel-Hagen, in 1900, was able to collect 42 cases of splenectomy for leukemia in which 4 patients temporarily recovered. Johnston, in 1908, collected 7 cases that had been reported between the years 1900 and 1908, with the temporary recovery of two patients. The total number of splenectomies for leukemia to the year 1908 was, therefore, 49, with the temporary recovery of only 6 patients. It is known that of the 6 patients who withstood the operation, 4 died later. One lived as long as eight months, another lived three and one-half years. From a practical standpoint, this experience meant a very prompt mortality of at least 96 per cent. Since the appearance of Johnston's paper, the sur-

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gical treatment of myelocytic leukemia has received almost no attention. McCown (1915) reported 2 cases in which operation was done after preliminary treatment by means of arsenic and the x-ray. There was marked improvement in these patients three months after operation. The total number of cases reported in the literature to Jan. 1, 1918, was therefore, 51, with 8 temporary recoveries, an operative mortality of 83 per cent; 4 of the 8 patients are known to have died later, giving a total known mortality of 93 per cent. Carstens has collected abstracts of 100 cases of splenectomy up to the year 1915. His article forms a complete and instructive résumé of the subject; he presents protocols of many of the published cases of splenectomy for myelocytic leukemia.

The remarkable remissions in the course of myelocytic leukemia which can be produced by means of the exposure of radium element, or radium emanations over the enlarged spleen, have been recently discussed by Ordway, Peabody and myself. The fact that the improvement following radium exposures occurred as a result of treatment over the spleen only, and not over the long bones or over any other structures, led to the inference that possibly a malfunction of the spleen might have more to do with the general condition of the patient than had been supposed. Moreover, if the spleen could be removed at a time when it was small and freely movable, and when the general condition of the patient was good, the operative mortality would doubtless be much less than it had been formerly. Again, the elimination of the spleen as the mechanical factor would remove one of the most troublesome features of the disease, and add to the patient's comfort. Naturally, in the light of the fatal former experiences, it was with considerable hesitation that splenectomy for myelocytic leukemia was resumed. The surgical treatment of leukemia has been discussed recently by W. J. Mayo and Balfour.

#### REPORT OF CASES

In August, 1909, at the Mayo Clinic the spleen was removed from a man forty-five years of age (Case 27414) whose leukocyte count was 11,000, and whose differential count showed no myelocytes. In August, 1911, two years later, the leukocytes were 64,500, with 14 per cent myelocytes. The patient died Dec. 27, 1914, five years and four months after the operation, with the symptoms of cardiorenal insufficiency. The spleen in this case weighed 2500 grams. This was evidently a leukemia of a more chronic type, as splenomegaly had been present four years preceding the operation. The total length of the history was

therefore, at least nine and one-half years. In view of the condition of the patient at the time of the operation it is possible that life was prolonged and the patient made more comfortable by splenectomy.

Sept. 2, 1916, a spleen weighing 1100 grams was removed from a woman aged fifty-six years (Case 171009). There had been no previous treatment by means of radium or the x-ray. The leukocyte count was 203,000, with 4.7 per cent myelocytes. Thirteen days after splenectomy the count had become reduced to 47,400, with 15.7 per cent myelocytes. The leukocytes rose to 113,800, with 36 per cent myelocytes, two months after operation. The patient was in good general condition up to three hours prior to death, which occurred one year and three months after operation and was probably due to cerebral hemorrhage. The total duration of the history in this case was approximately 3.5 years.

Twenty patients with myelocytic leukemia have been splenectomized at the Mayo Clinic. The two patients just discussed did not have preliminary treatment by means of radium. The remaining 18 patients, however, were treated by means of radium exposures over the spleen prior to splenectomy. The details of this method of treatment have been discussed in a former paper.<sup>6</sup> The spleen in each case of this series of 18 was very much reduced in size and the general condition of the patient was very much improved as the result of radium treatment. The 18 patients have been operated on within the last eighteen months, the last one Jan. 21, 1918.

The operation itself has not proved difficult in cases of leukemia when the spleen was only moderately large; there have been few adhesions and but little hemorrhage. Postoperative complications have been absent save in one patient who died with peritonitis. Postoperative transfusion was necessary only once.

The operative mortality for the entire group of 20 cases was one death, or 5 per cent. The operative mortality in the reported cases was 86 per cent. It is clearly demonstrated, therefore, that the operative mortality need not be high with proper preliminary preparation of the patient by medical means. A mortality of 5 per cent is lower than the average for splenectomy in general. Patients in remissions with only moderately large spleens are not serious operative risks, even though they had formerly had various forms of hemorrhage.

Of the remaining 19 patients who recovered from operation, 9 have since died, from two months to one year and three months after operation (leaving out of account the early chronic case in which the patient

lived five years and four months, with a total duration of history of (years and six months). The total duration of history in eight of the fatal cases was from nine months to three years and six months. In 7 of the 8 it was more than two years.

The length of life following splenectomy seems to vary with relation to the previous duration of the disease. Eight of the 9 patients dying subsequent to operation presented a duration of the disease of more than two years, while 6 of 10 living patients presented a total duration of disease of less than two years. Two living patients had a chronic type of the disease, and presented a duration of symptoms of more than ten years and more than six years, respectively. Aside from the chronic cases, then, when splenectomy has been performed there is no reason to infer that the disease runs more than its usual course of two or three years.

Seven patients were operated on early in the disease; that is, less than six months from the time of definite onset; 6 of these are alive. 5 are in excellent or very good condition. It is possible, though not likely, that in these early cases the results will be better than in the later ones; 4 of the 6 patients have already lived more than one year. Nothing, however, of a definite nature can be inferred from the fact that 6 of the 7 are alive, inasmuch as the total duration of the disease in all of them is less than two years.

It is worthy of note that in two cases of a chronic type the patients are alive ten months, and one year and seven months, respectively, after splenectomy. The total duration of disease in these two patients has been six years and ten months, and ten years and seven months, respectively. The spleens were large and fibrous and the leukocyte counts were not very high. Indeed, splenectomy may prove warranted in the very chronic types of the disease, from the standpoint of the patient's comfort, even though it be ineffectual in the prolongation of life.

The ages ranged from twenty-four to fifty-six years and seemed to make no difference in mortality. In general, patients with the largest spleens at the time of operation have died first. This would probably indicate that these patients represented a more severe type of the disease. The average weight of the spleens of the patients who were first treated by radium, and who have died since splenectomy was performed, was 975.6 grams. On the other hand, those with the smallest spleens at the time of operation have, in general, lived the longest. The aver-

weight of the spleens of these patients was 722.5 grams. Of 12 patients who lived one year or more after splenectomy, the average weight of the spleen at the time of operation was 800 grams; in 9 patients who had had a very thorough course of radium treatment it was 1500 grams.

A period of improvement in the patient's general condition followed operation in all cases save 3. This general improvement consisted of a feeling of well being, which may have been psychic, of an improvement in the appetite and the anemia, of a gain in weight, and a definite loss of the icteroid tint when it was present. The general condition in most instances was quite satisfactory before operation, so it can not be said definitely that splenectomy was the factor responsible for immediate improvement. Marked gain in weight was, however, almost a constant postoperative feature. The period of improvement was not of definite duration.

The blood, after splenectomy, showed no definite alteration, with the exception of an increase in the relative percentages of both small and large "lymphocytes." This was apparently not secondary to the alteration of the leukocyte count itself. Its significance is undecided, and the characteristics of these mononuclear cells require further study. It is to be learned whether they are of bone-marrow origin or whether splenectomy in reality stimulates the activity of lymphopoietic structures. In some instances there is a very marked decrease, temporarily, in the number of myelocytes found after splenectomy.

Two patients returned for observation after operation, and on examination were found to have enormously enlarged livers, which, however, gave no discomfort. The general condition and color of one of them were quite good.

One patient (Case 180499) who died two months after operation, and who had presented very slight enlargement of the glands, developed a remarkable glandular hypertrophy immediately after the operation, which persisted to the time of his death. The leukocyte count rose to 466,000, of which 63 per cent were small lymphocytes and 18.7 per cent were large lymphocytes, with only 3 per cent myelocytes. Before operation the small lymphocytes were as low as 3 per cent, with 28.3 per cent myelocytes. The small lymphocytes rose steadily, however, after radium treatment to the time of operation, when they were 39 per cent with 0.3 per cent myelocytes. Two weeks after operation the small lymphocytes rose to 61.7 per cent, and if the case had then been

seen for the first time it would doubtless have been diagnosed as lymphatic leukemia. Examination for oxidase granules in these was not made. A gland examined microscopically after death showed lymphocytic hyperplasia.

A detailed conception of the results following splenectomy may be obtained from an examination of Tables 1 and 2.

TABLE 1.—SPLENECTOMY FOR MYELOCYTIC LEUKEMIA

CASE	AGE	SEX	LEUKOCYTES, TIME OF OPERATION	DATE OF OPERATION	WEIGHT OF SPLEEN GRAMS	DEATH, TIME AFTER OPERATION	DURATION OF DISEASE
216648	36	F	22000	1-21-18	1705	Operative mortality 6 days	1 yr.
27414	45	M	11000	8-11-09	1514	Subsequent mortality 5 yrs. 4 mos.	9 yrs. 6 mos.
171009	56	F	203000	9- 2-16	1100	1 yr. 3 mos.	3 yrs. 6 mos.
173772	35	M	7800	12- 8-16	740	1 yr.	2 yrs. 6 mos.
175791	24	F	9000	1-18-17	750	4 mos.	2 yrs.
176684	26	F	13200	2-28-17	560	1 yr. 2 mos.	2 yrs.
162899	32	F	37900	3- 8-17	1000	3 mos.	9 mos.
189262	50	F	22000	4-10-17	1340	8 mos.	3 yrs.
180499	42	M	5600	5-11-17	1300	2 mos.	2 yrs.
204838	53	M	11400	8-17-17	410	3 mos.	2 yrs. 3 mos.

TABLE 2.—SPLENECTOMY FOR MYELOCYTIC LEUKEMIA: SUBSEQUENT CONDITION OF LIVING PATIENTS

CASE	AGE	SEX	LEUKOCYTES, TIME OF OPERATION	DATE OF OPERATION	WEIGHT OF SPLEEN, GRAMS	CONDITION	TIME AFTER OPERATION	DURATION OF DISEASE
168742	46	M	16400	9-19-16	2500	Good	1 yr. 7 mos.	10 yrs. 7 mos.
173312	33	M	3800	11-24-16	890	Excellent	1 yr. 6 mos.	2 yrs. 6 mos.
160937	37	F	68000	12-13-16	338	Good	1 yr. 5 mos.	3 yrs. 5 mos.
175574	37	M	15200	1-13-17	500	Excellent	1 yr. 3 mos.	1 yr. 5 mos.
169876	36	F	8400	1-27-17	220	Fair	1 yr. 3 mos.	1 yr. 6 mos.
177183	28	F	54400	2-17-17	440	Good	1 yr. 2 mos.	1 yr. 8 mos.
181494	19	F	7500	3-15-17	410	Excellent	1 yr. 1 mo.	1 yr. 7 mos.
186558	50	F	7200	4- 9-17	387	Good	1 yr.	1 yr. 6 mos.
193829	29	M	17000	6- 4-17	1320	Good	10 mos.	6 yrs. 10 mos.
199386	29	F	26000	7-26-17	220	Excellent	9 mos.	11 mos.

May 1, 1918.

### SUMMARY

1. Twenty patients with myelocytic leukemia have been splenectomized—18 of them after preliminary treatment by means of radium exposures over the spleen. The spleen and the leukocyte count were very

much reduced by means of radium, and the general condition of the patients was greatly improved.

2. One patient died—an operative mortality of 5 per cent. The operative mortality of cases reported in the literature in which little or no preliminary medical treatment had been given was 86 per cent.

3. Ten of the 20 patients are living in good general condition from nine months to one year and seven months following splenectomy. However, these patients have not yet outlived the life expectancy for the disease.

4. Of 7 patients operated on within six months of the time of the onset of the disease, 6 are alive.

5. It is probable that, at least in certain chronic types of myelocytic leukemia with fibrous spleens and relatively low leukocyte counts, splenectomy may be justifiable for the comfort of the patient.

6. A review of the cases at this time reveals no evidence that the duration of the disease is altered in any definite way by splenectomy.

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**HEART**



## ARBORIZATION BLOCK\*

F. A. WILLIUS

Arborization block or impaired intraventricular conduction is dependent upon graphic records for its recognition. It is now generally accepted to indicate disease of the subendocardial myocardium<sup>4</sup> and evidences serious functional cardiac disturbance.<sup>5</sup> The involvement occurs in the subendocardial or Purkinje plexus.

The deflections constituting the initial ventricular complex of the electrocardiogram are termed Q, R, and S, and indicate the passage of the electric impulse through the main divisions of the auriculoventricular bundle and their arborizations. These deflections comprise a graphic record which is upright in all leads, is abruptly pointed, and has a narrow base. The normal base width does not exceed 0.10 second.<sup>3</sup>

Arborization block is recognized by abnormal deviations of the Q, R, S group. These are increased width, notching of the apex, and splintering of the ascending and descending limbs.

The bizarre complex of arborization block is probably due either to impulse transmission through circuitous and aberrant paths or to delayed transmission through normal channels. Experimental and clinical evidence supports the former view. The abnormal complex, constituting the ventricular premature contraction (extrasystole), is well recognized, as is the complex of ventricular tachycardia and the idioventricular complex of complete auriculoventricular dissociation, which simulate the notched and widened Q, R, S group of arborization block. These we know result from ectopic stimuli which arise somewhere in the ventricular musculature and traverse aberrant paths to provoke ventricular systoles. The constancy in form of the deflections of the normal electrocardiogram make the abnormal complexes stand out as striking entities.

This study was undertaken to determine, if possible, the significance of this disordered mechanism with especial reference to life expectancy.

\* Reprinted from Arch. Int. Med., 1919, xxiii.

One hundred and thirty-eight patients with arborization block have been examined. The electrocardiographic requirements warranting the

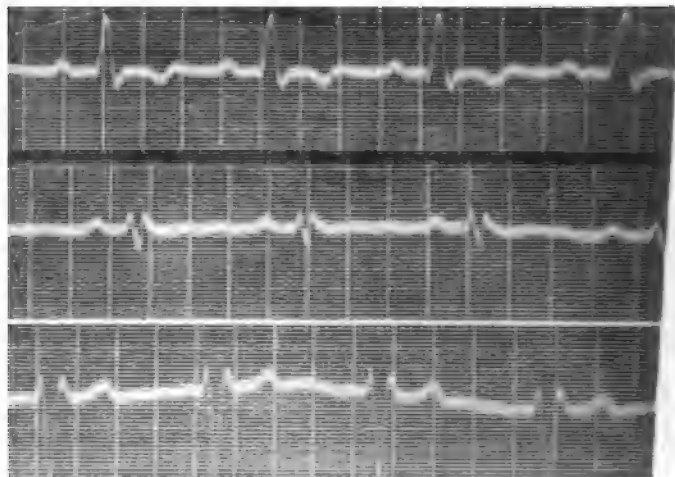


Fig. 168.—Rate 65. Q, R, S complex widened in Leads 1 and 3. 0.11 Sec. and splintered in Lead 2. Inverted T wave Lead 1. Left ventricular preponderance. Case 160997.

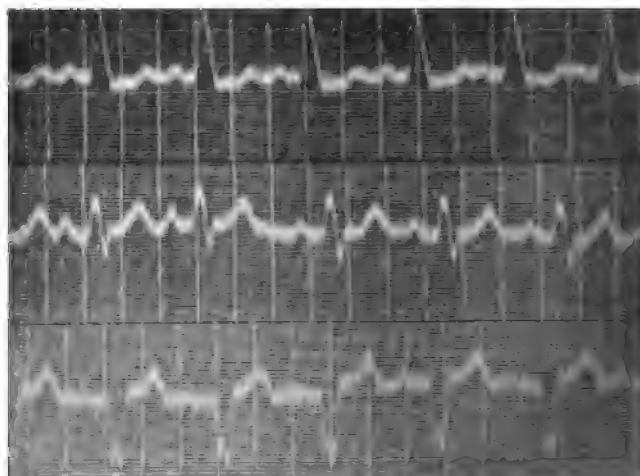


Fig. 169.—Rate 100. Q, R, S complex notched and widened 0.12 sec. Left ventricular preponderance. Case 213193.

diagnosis were—(1) notching of the apex R; (2) splintering of the ascending or descending limb; and (3) in complexes of normal contour, a base width exceeding 0.10 second. These changes are summarized in Table 1.

TABLE 1.—Q, R, S COMPLEX CHANGES

[illegible]

The electrocardiograms illustrate the types represented (Figs. 167-177). The tension of the galvanometer fiber influences the width

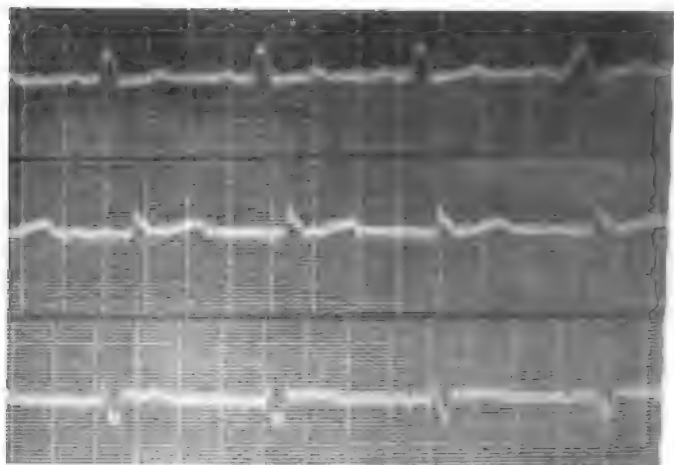


Fig. 170.—Rate 66. Q, R, S complex notched. Left ventricular preponderance. Case 15476.

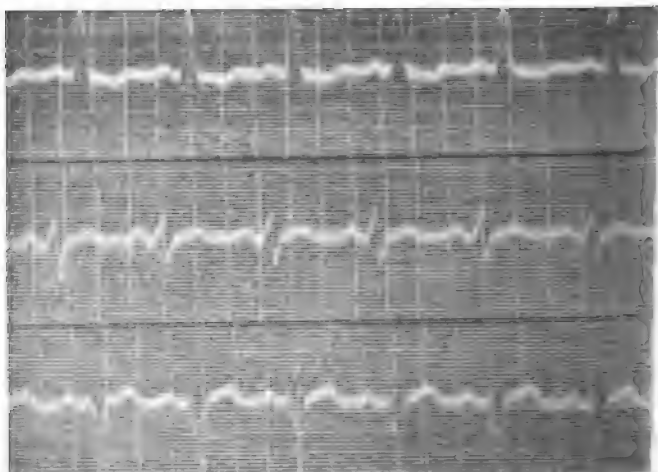


Fig. 171.—Rate 82. Q, R, S complex splintered and widened 0.11 sec. Left ventricular preponderance. Case 185664.

the unaltered complex; a loose fiber is capable of giving an increased base width.<sup>2</sup>

The disorders responsible for the development of subendocardial myocardial disease are—(1) infections; (2) degenerative processes

and (3) local nutritional disturbances. These observations are summarized in Table 2.

• TABLE 2.—ETIOLOGIC DISEASES

DECADE	ENDOCARDITIS	PERCENTAGE	CARDIOVASCULAR RENAL	PERCENTAGE	THYROTOXIC ADENOMAS	PERCENTAGE	EXOPHTHALMIC GOITER	PERCENTAGE	ATHEROSCLEROSIS	PERCENTAGE	LUES	PERCENTAGE	NO ETIOLOGIC HISTORY
11-20	2	100	0	0	0	0	0	0	0	0	0	0	0
21-30	8	80	1	10	0	0	1	10	0	0	0	0	0
31-40	5	62.5	0	0	0	0	0	0	0	0	1	12.5	2
41-50	14	45.2	10	32.3	0	0	1	3.2	0	0	2	6.5	6
51-60	10	24.4	14	34.1	6	14.6	2	4.8	0	0	1	2.4	9
61-70	8	20.5	17	43.6	2	5.1	1	2.6	2	5.1	0	0	9
71-80	2	28.6	2	28.6	1	14.2	0	0	1	14.2	0	0	1
	49		44		9		5		3		4*		27

\* Three cases under lues classified under endocarditis.

Endocarditis was the most frequent causative disorder and occurred in 49 of the 138 cases (35.5 per cent). Its predominance in the earlier decades of life was anticipated; degenerative and local nutritional dis-

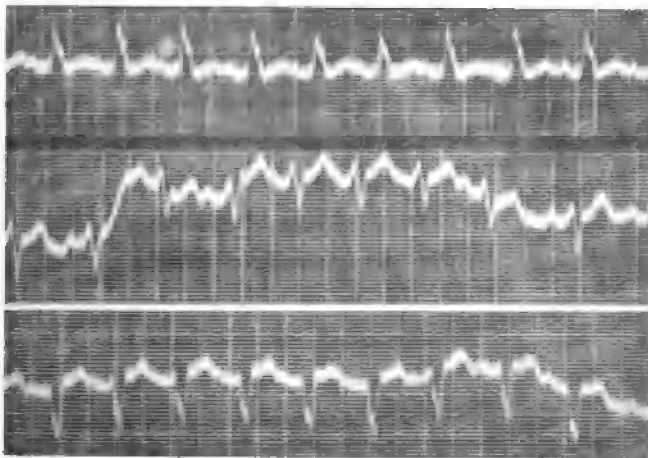


Fig. 172.—Rate 112. Q, R, S complex splintered and widened 0.12 sec. Left ventricular preponderance. Case 176302.

turbances dominate the later decades. In order of frequency are cardiovascular-renal disease with hypertension, thyrotoxic adenomas, and



arteriosclerosis. Exophthalmic goiter occurred in five cases. Only four proved cases of lues were found. In 27 instances no tangible histories or findings suggesting causative factors were obtained.

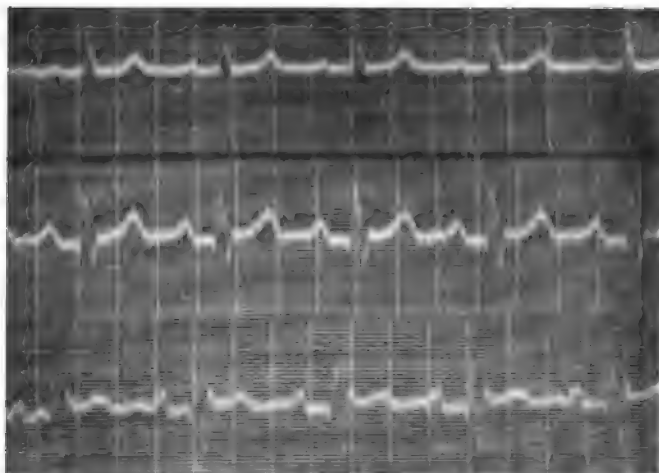


Fig. 173.—Rate 75. Q, R, S complex splintered 0.08 sec. Left ventricular preponderance. Case 162663.

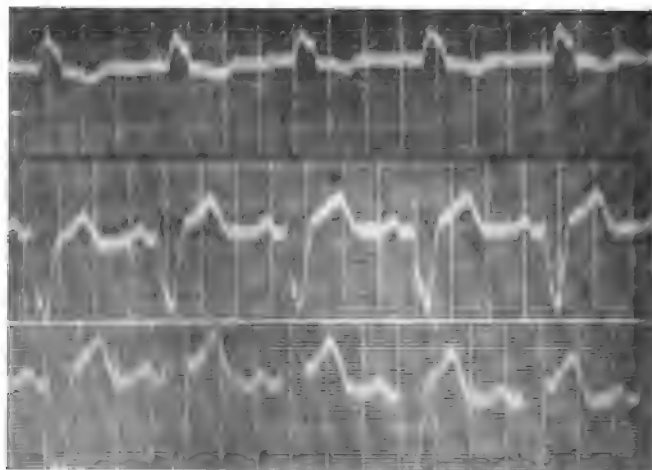


Fig. 174.—Rate 82. Q, R, S complex notched and widened 0.14 sec. Inverted T wave Lead 1. Left ventricular preponderance. Case 216281.

Exertion dyspnea was a complaint in all cases, and in 31 (22.5 per cent) orthopnea was a dominant symptom. Palpitation on exertion was present in 47 instances (34 per cent). Twenty-two patients (15.9 per

had angina pectoris, and in five of these this occurred in aortic disease. Edema of the lower extremities varying from slight pitting in a few instances to definite swelling with glazed skin in a few number, present in 42 patients (30.4 per cent). Only five cases of general

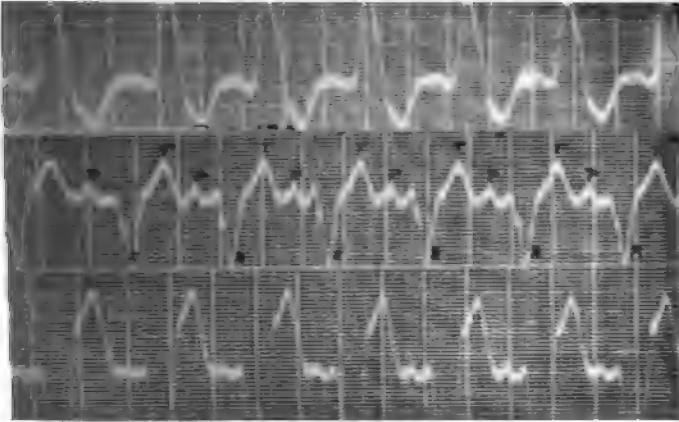


Fig. 175.—Rate 115. Q, R, S complex splintered and widened 0.16 sec. Inverted T wave Lead 1. Left ventricular preponderance. Case 143010.

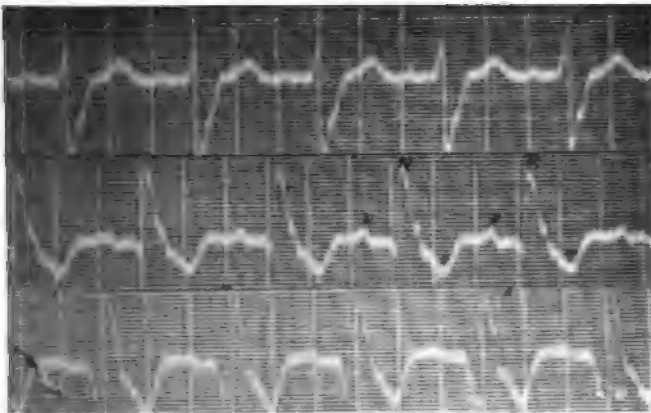


Fig. 176.—Rate 86. Q, R, S complex notched, splintered and widened 0.12 sec. Inverted T wave Leads 2 and 3. Right ventricular preponderance. Case 142737.

anasarca are recorded in this series. Of the edema cases 24 (57.1 per cent) occurred in patients with endocardial valvular disease. The relative infrequency of edema in grave heart disease is very interesting, and emphasizes the importance of adjunct methods in the thorough examination of patients suffering from cardiac disease.

Objectively, the striking feature present in practically all the cases is the lack of definition of the heart sounds. They are muffled, the normal differentiation between the first and second sounds is absent, the auscultatory findings of embryocardia are simulated. There is an increase in cardiac dullness in most of our cases, both to the right and to the left of the midsternal line. Auricular fibrillation was present in 18 cases (13 per cent) and occurred, except in one instance, in the last decades of life. Four patients had delayed auriculoventricular conduction, that is, P-R intervals exceeding 0.22 second. The deflection amplitudes of the Q, R, S group showed that 64 patients (46.4 per cent) had normal values (10 to 15 millivolts), 61 patients (44.2 per cent) had



Fig. 177.—Rate 75. Q, R, S complex notched and widened 0.16 sec. Inverted T wave Lead I. Left ventricular preponderance. Case 154081.

values, the greatest 39 millivolts, and 13 patients (9.4 per cent) had low values, the lowest of which was 5 millivolts. Deflections of high amplitude, largely diphasic, are believed by Carter to be indicative of a definite, totally obstructive, temporary or permanent lesion of one of the branches of the auriculoventricular bundle; those of low amplitude suggest diffuse sclerosis, although they do not preclude localized lesions of the main branch and its arborizations.

No striking changes in amplitude of the final wave T of the ventricular complex were noted. This wave was negative in 85 cases (63 per cent) and occurred most frequently in Lead I alone, in 42 cases (49.4 per cent). Table 3 shows the T wave negatively in this series. The

inversion of the T wave in Lead I is significant, I believe, and of itself indicative of myocardial changes, for in all the electrocardiograms studied in which this observation was noted the patients presented definite clinical evidence of myocardial insufficiency, except in one case, in which the conclusions were indefinite.

TABLE 3.—T WAVE NEGATIVITY

DECADES	L. I	L. 2	L. 3	L. 1 AND 2	L. 2 AND 3	L. 1, 2, AND 3
11-20	1	0	0	0	0	0
21-30	0	1	2	2	1	0
31-40	1	0	3	1	0	0
41-50	8	0	1	2	2	0
51-60	14	0	3	3	6	1
61-70	16	0	3	5	1	4
71-80	2	0	0	1	1	0
	42	1	12	14	11	5 85

One hundred and twelve patients with arborization block have been heard from in answer to letters of inquiry. Seventy-eight (69.6 per cent) of these have died; all except three died of heart disease. The average duration of life from the time of examination was eight and one-half months. These statistics bear out the presumption that arborization block is a grave disorder. It is well recognized that disease involving the conduction system is a serious menace to life, but arborization block is attended by an earlier mortality than that caused by the lesions higher up. As life is directly dependent on ventricular action, any impairment of ventricular function is grave. The deaths are summarized in Table 4.

TABLE 4.—SUMMARY OF DEATHS

DECADE	TOTAL CASES	DEATHS
11-20	2	1
21-30	10	3
31-40	8	5
41-50	31	16
51-60	41	24
61-70	39	23 (died of cancer and pneumonia)
71-80	7	6 (died of cancer)
Total	138	78

Thirty-four patients of the series are known to be alive; of these, 17 are worse, 4 of them bedridden; 9 report their conditions unchanged

and 8 report some improvement. We were afforded the opportunity of 5 necropsies—the cardiac findings are appended. No definite localized lesions were found, but rather diffuse degenerative processes involving the myocardium.

**CASE 1 (180119).**—Very marked fatty changes in the myocardium; marked dilatation of the aortic, mitral, and tricuspid valvular rings of the heart; moderate nodular fibrous and fatty thickening of the lining of the aorta and of the aortic and mitral leaflets of the heart; marked thinning of the myocardium of the left ventricle; marked dilatation and engorgement of all of the chambers of the heart; moderate hydropericardium. Histologic findings: Fragmentation and slight fatty changes.

**CASE 2 (147045).**—Obliterative fibrous adhesive pericarditis; marked nodular sclerosis and fatty changes in the lining of the aorta and its main branches; marked calcareous sclerosis of the coronary arteries; huge spontaneous thrombosis of the dependent portion of the left ventricle; marked hypertrophy of the myocardium of the left ventricle; marked dilatation of all the chambers of the heart; moderate dilatation of the aortic and mitral valvular rings; marked diffuse thickening of the pulmonary artery. Histologic findings: The pericardium was thickened and adherent to the heart. There was a marked replacement of the heart muscle by fibrous tissue. Toward the lower portion was seen hyalinization of the muscle. The thrombus was made up of fibrin, and in places showed a slight infiltration of leukocytes. With the fat stain considerable fat was found in the thrombus.

**CASE 3 (161776).**—Marked fatty degeneration of the myocardium; marked hydropericardium; moderate dilatation of the heart. Histologic findings: In the heart there were marked fatty degeneration and fragmentation; moderate increase in fibrous connective tissue and hypertrophy of the muscle.

**CASE 4 (189701).**—Acute dilatation of the heart; marked fatty and fibrous sclerosis of the lining of the aorta and of the aortic and mitral valvular leaflets; petechial hemorrhages in the visceral pericardium. Histologic findings: Moderate diffuse fatty degeneration of the myocardium. Aortitis probably luetic; fibrous and fatty changes in the intima and media, with round cell infiltration.

**CASE 5 (197468).**—Marked fatty and fibrous diffuse parenchymatous myocarditis; marked hypertrophy of the myocardium of the left ventricle; marked dilatation of all the chambers and valvular rings of the heart; spontaneous mural thrombosis of the left ventricle; slight hydropericardium. Histologic findings: Fatty and fibrous degeneration of the myocardium.

## SUMMARY

Arborization block is a grave disorder of the cardiac mechanism; it entails a large and early mortality (69.9 per cent), in an average duration of eight and one-half months.

Disorders responsible for the development of this condition were found to be, in order of frequency—(1) infections; (2) degenerative diseases, and (3) local nutritional disturbances.

The relative infrequency of edema was a striking observation.

The lack of definition and differentiation between the first and second heart sounds was constantly observed.

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# CONGENITAL DEXTROCARDIA\*

F. A. WILLIUS

Anomalies of the heart, partly because of their infrequent occurrence and partly because of their occult manifestations, are of particular interest to the clinician. I have recently been afforded the opportunity of observing three cases of congenital dextrocardia. Two types of the anomaly are recognized; one associated with transposition of the abdominal viscera (*situs transversus*), and the other in which the transposition affects only the heart and great vessels. At times<sup>3</sup> anomalous arrangement

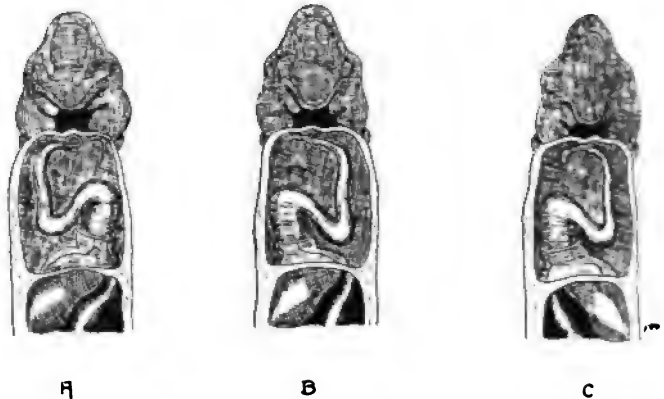


Fig. 178.

ment of the venæ cavæ permits the admixture of arterial and venous blood; this gives rise to a clinical picture simulating the syndrome of congenital heart disease.

Recalling the embryologic development of the heart, it is readily seen how transposition of this organ occurs. The two primitive cardiac tubes fuse into one about the fifteenth day,<sup>2</sup> and an auricular, ventricular, and bulbar subdivision becomes evident (Fig. 178). The tube soon becomes bent on itself, which determines largely the future axis

\* Presented for publication November 29, 1918. Reprinted from *Am. Jour. Med. Sci.*, 1919, clvii. Copyright by Lea & Febiger.

of the heart. In congenital transposition the primitive tube bends in a contra-sigmoid ( $\omega$ ) instead of the normal sigmoid (S) manner. This has been explained<sup>1</sup> by assuming that the embryo lies in an abnormal position within the chorion so that its right side, instead of its left, lies closer to the blood supply. The three patients whom I examined presented the most frequent anomaly, dextrocardia with *situs transversus*. In no instance was there any complaint referable to the abnormality.



Fig. 179.

#### REPORT OF CASES

**CASE 1 (222329).**—A woman, aged forty years, presented herself for examination complaining of chest pains of the intercostal neuralgic type. The apex-beat of the heart was palpable in the fifth right intercostal space, 7.5 cm. from the midsternal line. The cardiac dullness extended 9 cm. to the right and 1.5 cm. to the left of the midsternum. The heart-sounds were best heard at the apex. Liver dullness was found to be on the left side, and gastric tympany on the right. The systolic blood-pressure was 152, the diastolic was 90. Radiograms of the chest



showed the dextrocardia, and a transposition of the stomach and colon (fluoroscopic colon). The electrocardiogram showed the heart-rate to be 94. Complete inversion of Leads I and II. The amplitude of the R waves in Leads I and II exceeded those in Lead III by one-third (179, 180, and 181).

CASE 2 (224506).—A woman, aged thirty-seven years, presented herself for examination on account of a pelvic complaint. The apex of the heart was palpable in the sixth right intercostal space, 9 cm. from



Fig. 180

the midsternal line. The cardiac dulness extended 11 cm. to the right of the midsternum. The heart-sounds were best heard at the apex. Liver dulness was found on the left side and gastric tympany on the right. A bilateral salpingitis and a cyst of the left ovary were palpated. The systolic blood-pressure was 120, the diastolic was 75. The radiograms revealed dextrocardia and transposition of the stomach and colon (fluoroscopic colon). The electrocardiogram showed the heart-rate to be 75. There was complete inversion of Lead I. The amplitude of the R waves in Lead I were practically the same as those in Lead II and

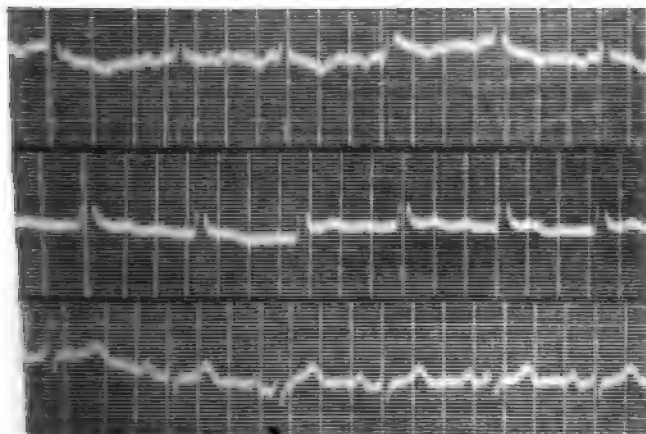


Fig. 181.

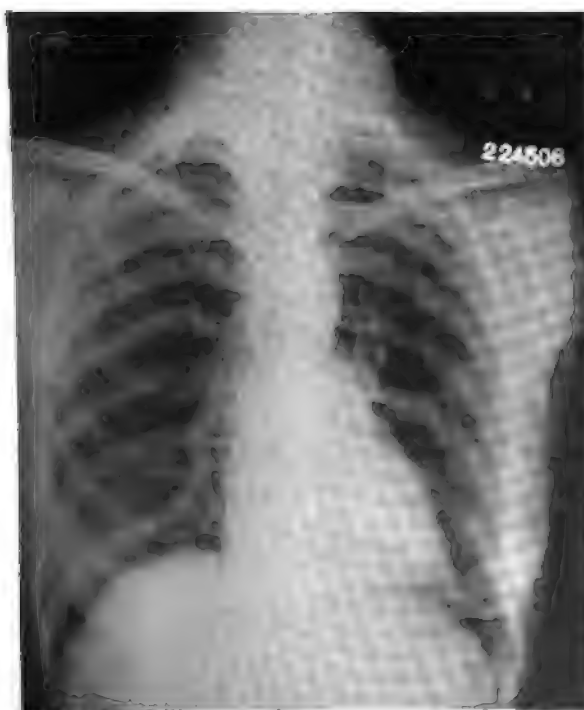


Fig. 182.



Fig. 183

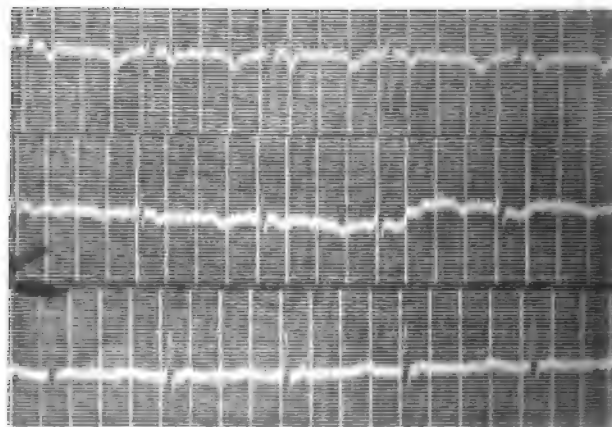


Fig. 184.

ded those in Lead III by slightly more than a third (Figs. 182, and 184).

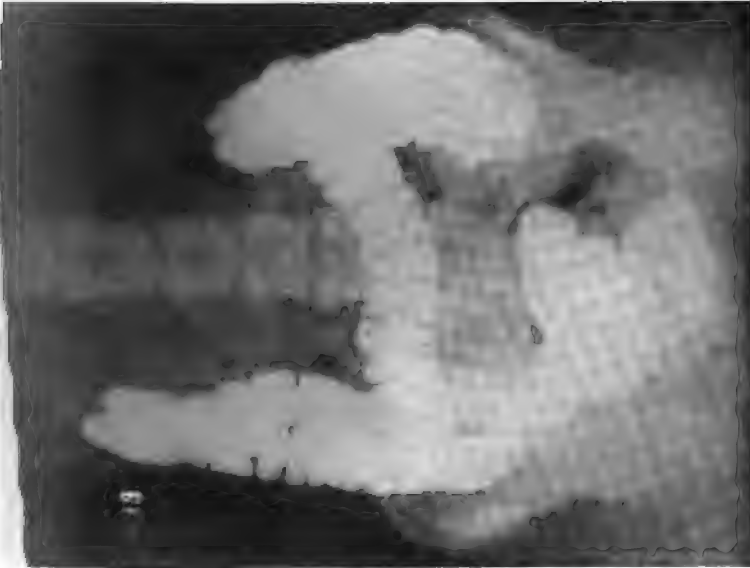


Fig. 186.

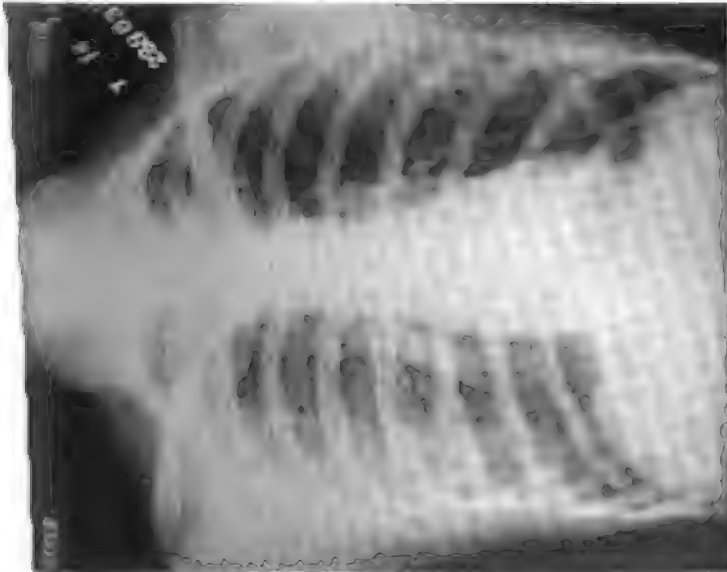


Fig. 185.

CASE 3 (238633).—A woman, aged thirty-three years, presented herself for examination on account of goiter. The heart, as in the other

cases, was found to be on the right side. The liver dulness was found on the left side and the gastric tympany on the right. The patient had a single adenoma of the right lobe of the thyroid, 4 by 4.5 cm. The systolic blood-pressure was 112; the diastolic was 78. The radiograph revealed dextrocardia and transposition of the colon. The electrocardiogram showed the heart-rate to be 115; there was complete inv

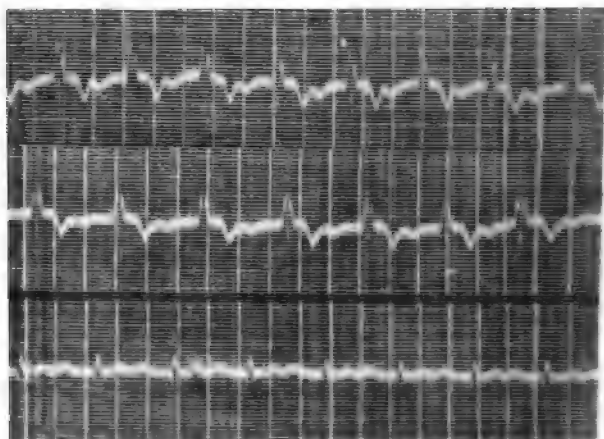


Fig. 187.

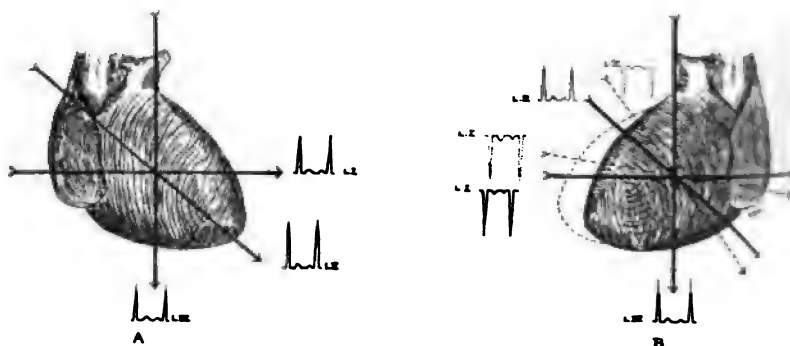


Fig. 188.

sion of Lead I, and the amplitude of the R waves in Lead I were diminished to about one-half those of Lead III. The amplitude of the R waves in Lead III slightly exceeded those in Lead II. There was evidence of left ventricular preponderance (Figs. 185, 186, and 187).

The electrocardiograms of the last two cases essentially confirm the findings recorded in previous publications.<sup>4, 5, 7, 8</sup> Lead I shows a

complete inversion of all the deflections. Fig. 188 illustrates the angles produced by the direction of the leads and the resulting electrocardiograms. Case 1 (222329) shows the inversion also involving Lead II, and is explained by an exaggeration of the inclination of the cardiac axis to the right. The leads represent fixed planes of electric potential, and changes in cardiac position or alterations in muscle bulk preponderance obviously affect the electric currents, as expressed by the electrocardiogram.

It has been mentioned<sup>8</sup> that the R wave in Lead III becomes taller than in Lead II, but in these reported cases no constancy was observed. Hirschfelder mentions that the electrocardiographic curves sometimes are practically normal. Inversion of the deflections in Lead I is definite evidence of congenital dextrocardia with *situs transversus*, and we recognize electrocardiography as a valuable adjunct in the differential diagnosis of cardiac displacements.

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stand strain well. In this group, 104 patients have been operated with 4 deaths. One patient died following a Porter hot-water injection and 3 following thyroidectomy. Of the latter, 2 died of hyperthyroidism and 1 of myocardial insufficiency on the second day after operation. Ten patients were under thirty, 20 between thirty and forty, and 74 were more than forty years of age. The operative mortality was 4 deaths in 104 cases (3.8 per cent), which compares favorably with the normal operative mortality of 2.6 per cent.

*Thyrototoxic adenomas.*—Many patients having adenomas (simple goiter) for a certain number of years develop symptoms of thyrotoxic intoxication. The onset of symptoms is frequently insidious and the initial subjective complaints are those of a failing myocardium. The patients are usually older, beyond forty years of age, and as I have mentioned, the heart muscle does not tolerate toxic influences well. Added to this is an insidious onset. This group presents many cardiac paths. Experience has shown that such patients so often show striking cardiac improvement following thyroidectomy that the added risk seems fully justified. All patients with fibrillation are, however, subjected to preliminary medical treatment which is continued after operation if the case demands it. Thirty-six patients with fibrillation had thyroidectomies; the one operative death gives a mortality of 2.7 per cent. The normal operative mortality in this group is 2.8 per cent. The favorable showing is owing largely to preoperative therapy and to the correlation between the surgical and medical services.

*Other conditions.*—There were 10 cases of fibrillation in patients less than forty years of age and 20 in those more than forty years of age, constituting a total of 30 cases in which operative measures were employed. The operations were as follows: 12 tonsillectomies, 4 excisions of epitheliomas (2 lower lip, 1 glands of the neck, and 1 larynx), 1 excision of glands for diagnosis (sarcoma), 3 cholecystectomies and appendectomies, 3 gastro-enterostomies (2 for ulcer and 1 for carcinomatous obstruction), 1 cholecystectomy, choledochotomy and appendectomy, 1 Talma-Morrison, 1 herniotomy, 1 cataract extraction, 1 suprapubic stab, 1 cauterization for urethral caruncle and 1 cystotomy and prostatectomy. There were 2 early deaths, 1 cardiac, following suprapubic stab, and 1 due to cholangitis following cholecystectomy.

*Auricular flutter.*—This cardiac disorder is recognized as being due to rapid coördinate contractions of the auricles, stimulated by foci of irritation located in the auricular wall outside the normal pace-maker

(sino-auricular node). The auricles contract at a rate of 200 to 380 per minute and the ventricles respond usually to one-half the auricular contractions, although any rhythm from a 1:1 association to a complete heart block may exist. The pulse is regular in one-half the reported cases and grossly irregular in the other half. The degree of block may vary from time to time and most patients are subject to paroxysmal "weak spells," owing to sudden decrease in the degree of block which allows the ventricles to assume full auricular rate. The condition is usually chronic and may exist for years.

Four patients have been operated on, all included in the foregoing under fibrillation. These patients are of particular interest as apparently being the first proved cases of flutter coming to operation. A previous report<sup>2</sup> showed that these four patients were subjected to vigorous digitalis therapy and rest until fibrillation was induced, and then operation was done.

Three of the patients had exophthalmic goiter, though one had a cholecystectomy and tonsillectomy in the clinic and a thyroidectomy, later, elsewhere. One other patient had had tonsillectomy. All the patients with exophthalmic goiter resumed a normal rhythm after operation, and two had no further cardiac symptoms. The last patient on whom a tonsillectomy was performed, reports himself greatly improved. Thus far there has been no mortality.

*Partial and complete heart block.*—One patient with complete block has had three operations in eleven years; appendectomy, radical amputation of the breast for carcinoma, and excision of recurring nodules of the skin. An electrocardiogram was taken before the last operation. The pulse was recorded as being unusually slow at the previous examinations. The patient is alive and quite well.

Ten patients showing delayed conduction between auricles and ventricles, that is, auriculoventricular intervals of 0.22 to 0.28 of a second, have been operated on as follows: 4 tonsillectomies, 1 double ligation of the superior thyroid vessels for exophthalmic goiter, 1 double ligation and subsequent thyroidectomy for exophthalmic goiter, 2 thyroidectomies for thyrotoxic adenomas, 1 cholecystectomy and 1 prostatectomy. Six were more than forty years of age and 4 were under forty years. The patient on whom prostatectomy was done died on the fourth day, presenting the cardiovascular renal syndrome.

*Intraventricular or arborization block.*—This condition is due to impaired conduction of the cardiac impulse after its passage through the



bifurcation of the auriculoventricular bundle and evidences disease of the main bundle branches and the subendocardial plexus. Oppenheimer and Rothschild have emphasized the gravity of this condition and its early fatality which it often indicates. The electrocardiogram reveals a prolonged Q, R, S interval and variations from slight notching to the unusual complexes which are ascribed to branch bundle defects. A striking observation in this group of cases is the uniformity with which the clinical findings are substantiated by the graphic records in revealing serious myocardial disease. Twenty patients have been operated on, under forty years of age and 13 more than forty years, without any operative mortality. There were 8 tonsillectomies, 5 thyroidectomies (3 for exophthalmic goiter and 2 for thyrotoxic adenoma), 1 salpingectomy, 1 cholecystectomy and appendectomy, 2 chest aspirations, 2 gland excisions for diagnosis (1 malignant and 1 inflammatory), and 1 posterior gastro-enterostomy for duodenal ulcer.

*Mitral stenosis.*—Seventy-three cases of mitral stenosis are recorded in which operations were done. Twenty-five of the patients were under forty years of age and 48 were more than forty years. As previously stated, valvular disease alone cannot be satisfactorily grouped because of the difficulty in accurately classifying the degree of myocardial insufficiency. This mitral lesion is recognized as being serious owing to its tendency to progression, and therefore the cases have been included in this report. An attempt has been made to estimate by clinical impressions the degree of decompensation present, and, while obviously inaccurate, it is necessary in presenting the type of case represented in this study. The scale of 1 to 4 (minimum to maximum) has arbitrarily been used in denoting the degree of decompensation. The average in patients under forty years of age was 2, in those more than forty, 2+. Ten patients showed auricular fibrillation (vide supra); 9 of these were patients more than forty years of age. The operations are as follows: 39 tonsillectomies, 17 thyroidectomies (10 for simple goiter, 4 for exophthalmic goiter, and 3 for thyrotoxic adenomas), and 4 of these patients had secondary operations, including 2 tonsillectomies, 1 appendectomy and 1 double cataract extraction. There were one double ligation of the superior thyroid vessels for exophthalmic goiter, 4 appendectomies, 1 cholecystostomy, 4 cholecystectomies and appendectomies, 1 cholecdochotomy, cholecystectomy and appendectomy, 1 subtotal abdominal hysterectomy, 1 perineorrhaphy, 1 trachelorrhaphy, 1 tumor excision (benign), 1 inguinal herniotomy, and 1 thoracic paracentesis. There was

no immediate operative mortality but one patient died two weeks later of cholangitis following a choledochotomy, cholecystectomy, and appendectomy. The mortality in this group is 1.3 per cent. It is impossible accurately to state the normal mortality in such a protean surgical list but 1.5 per cent seems very conservative.

*Aortic lesions.*—It has long been recognized that aortic disease needs no emphasis as regards its gravity. This group includes aortic valvular disease, aortitis and dilatation (not aneurysmal). Sixteen patients with aortic valvular disease have been operated on; 11 under forty years of age and 5 more than forty years. Six patients presented double aortic lesions, that is, insufficiency and stenosis, and 1 presented evidence of aortitis. One patient had aortic stenosis alone. These patients were all able to be up and about with relative comfort. Anginal pains were not elicited in a single instance. There were no operative deaths but 1 patient is reported dead from heart failure one year later (tonsillectomy). There were 12 tonsillectomies, 1 thyroidectomy for adenomas, 1 cholecystectomy, 1 double herniotomy and appendectomy, and 1 chest aspiration. Two patients with aortitis (not including the aforementioned case) were operated on; both were more than forty years of age. There were one exploration (general abdominal carcinosis) and 1 tonsillectomy. The latter patient died a cardiac death three months later. Four patients with dilatations of the aorta (not aneurysmal) underwent surgical procedures. The clinical diagnoses in these cases were verified by the fluoroscope. Three of the patients were more than forty years of age. There were 2 thyroidectomies for exophthalmic goiter, 1 tonsillectomy, and 1 cystotomy and herniotomy. There were no deaths.

#### SUMMARY

1. The decision of operability in cardiac disease depends on factors as follows: (1) The immediate operative risk; (2) the probable improvement of the heart after operation; (3) the patient's relative chance for length of life or general health with or without operation, and (4) in less serious conditions, whether the operative relief will justify the added risk.

2. Cases in which the heart permits the patient to go about in relative comfort, or in which it can be sufficiently restored by treatment to allow this, usually are considered safe for operation.

3. Malignancy complicated by heart disease is usually considered operable if a fair hope of cure is offered.

4. The best measure of operative risk is a good clinical impression of the patients' ability to stand physical strain, supplemented by a careful history and a thorough physical examination.

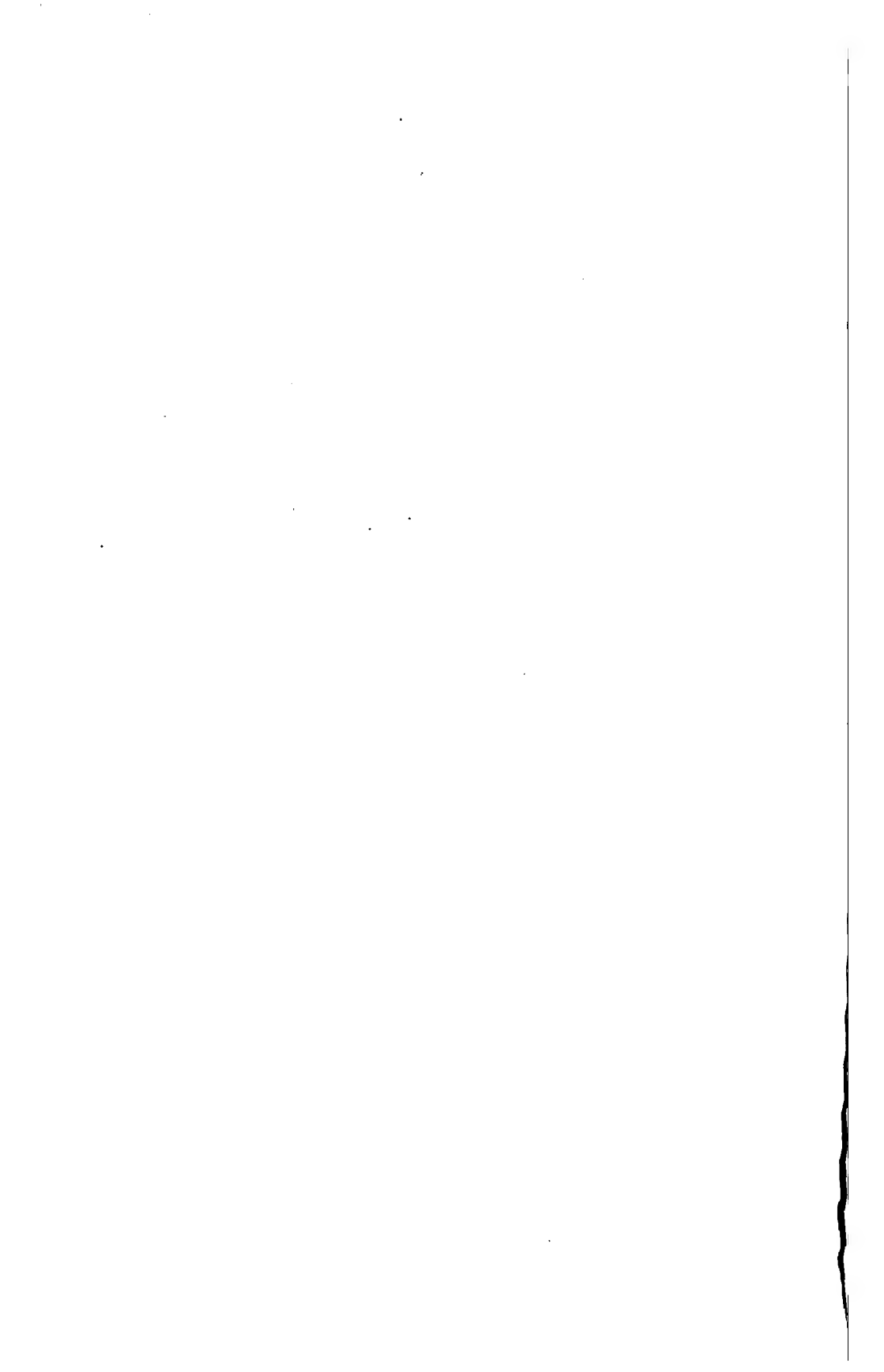
5. Preoperative medical therapy and rest combined with surgical and medical correlation after operation is of paramount importance.

6. The general tendency is to require too great a margin of cardiac safety in surgical work.

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**BLOOD**



## STUDIES ON CHOLESTEROL\*

### IV. EXPERIMENTS CONCERNING THE RELATION OF THE DIET, THE BLOOD CHOLESTEROL, AND THE "LYMPHOID DEFENSE"

GEORGINE LUDEN

In a series of experiments on myself made between June 17 and Dec. 30, 1916, I was able to observe a close relation as well as a reciprocal action between the diet, the blood cholesterol, and the lymphocytic reaction or "lymphoid defense." The term "lymphoid defense" was chosen in reference to the observations of Murphy and Morton, who found that animals on which cancer transplants did not "take" showed up to a 200 per cent increase in the lymphocyte count of their blood, while those not endowed with this natural resistance showed no such increase. When the lymphoid tissues were injured or partly destroyed by means of the x-ray 100 per cent of "takes" could be obtained. The term "lymphoid defense" will be used in this paper to represent the combined percentages of the small and the large lymphocytes in the differential counts. The transitionals have not been included, as hematologists do not agree concerning the place that should be assigned to them in the classification of the blood cells, though they may play a part in the reaction against malignant proliferation. Grawitz considers transitionals to be the prototypes of the polymorphonuclear neutrophil leukocytes, Simon classifies them with the large lymphocytes, and Ziegler<sup>58</sup> looks upon them as closely allied to lymphoid myelocytoid cells.

The relation observed between the diet, the blood cholesterol, and the lymphoid defense suggested that beneficial results might be obtained from dietary measures different from those we are accustomed to take into account. The practical importance of this relation may be gathered from the following considerations:

Murphy and Morton state that the "lymphoid crisis" which they describe is to be considered "not merely an accompanying factor in the

\* Reprinted from Jour. Lab. and Clin. Med., 1917, iii, 141-174.

immune period, but essential to the process." In other words, the lymphocytic reaction appears to be one of the body's natural means of defense against malignant proliferation. This assumption seems to be corroborated by Stevens' recent observations on a reactive lymphocytosis induced by the x-ray and followed by improvement in cases of malignant growth. The fact that "lymph-gland extract" is being tried against malignant tumors and conditions marked by new growth of tissue, also tends to show that Morton and Murphy's interpretation of the lymphocytic reaction is gaining acceptance in medical circles.

The physiologic activity of cholesterol and the cholesterol content of the blood have been the object of a great number of recent investigations as regards their relation both to normal growth and to various pathologic conditions, by Robertson,<sup>40</sup> Browder, Luden,<sup>28</sup> Robertson and Burnett,<sup>39</sup> Rothschild,<sup>42, 43, 44, 45</sup> Bloor,<sup>3, 4, 5, 6</sup> and others. Luden<sup>28</sup> has called especial attention to the effect of cholesterol retention on cell proliferation.

The influence of the diet on the cholesterol content of the blood, which had been studied previously in animals because of its relation to arteriosclerosis by McMeans, Saltykow and others, or its relation to the function of diverse organs (the adrenals, Krylow, Sternberg; the spleen, Soper; the liver, Chalatow, Rothschild, and others) has lately been given a clinical application by Rothschild in his work on the dietetic management of hypercholesterinemia in cases of cholelithiasis. This work shows that dietary measures calculated to reduce the blood cholesterol will relieve the symptoms of a group of patients to whom cholecystectomy, and often secondary operations, have brought only temporary relief.

So far as the writer is aware, the relation between the diet, the lymphoid defense, and the cholesterol content of the blood has never been studied, yet the deduction seems admissible that dietary measures calculated to reduce the blood cholesterol while stimulating the lymphocytic reaction might prove as beneficial in cases of carcinoma before and after operation as the regulation of the diet in cases of chronic hypercholesteremia after cholecystectomy. The good results obtained by postoperative treatment of malignant growths with radium and roentgen rays are well known, and Stevens' observations suggest that these results may be due to the lymphocytic reaction induced by the rays. In a small number of cases which the writer has had the opportunity to study, both radium and the x-ray appeared to increase the lympho-

cyte count while they lowered the cholesterol content of the blood. The latter observation was reported also by Luden<sup>28</sup> in connection with the effect of experimental x-ray treatment on the blood of goats. There is no reason to suppose that the activation of the lymphoid defense by dietetic measures should be less beneficial than that produced by means of radium or the x-ray. On the contrary, it is to be expected that therapeutic measures that keep within the bounds of normal physiologic activity, so to speak, will be less apt to tax the general health of a patient than any extraneous measures.

Before describing the experiments with which this paper is concerned, it will be necessary to discuss three factors that were bound to exert a great influence on the results obtained; namely, the individual cholesterol standard of the blood, the cholesterol content of certain articles of food, and the effect of digestion on the cholesterol content of the blood.

#### THE INDIVIDUAL CHOLESTEROL STANDARD OF THE BLOOD

Rothschild<sup>42</sup> has pointed out that normal animals have an individual cholesterol standard, the variations of which are slight. Luden<sup>29</sup> was able to corroborate these findings by observations on the cholesterol content of the blood of goats. Similar observations were made regarding the cholesterol value of normal persons partaking of an ordinary mixed diet. My own cholesterol standard was established by a series of determinations made between Nov. 23, 1915, and June 16, 1916 (Table I). It remained practically constant at 0.272 (90) mg. in 6 c.c. of chloroform extract made according to Bloor's original method<sup>3</sup> for the determination of blood cholesterol. The only considerable exception occurred during a very slight attack of appendicitis, when the cholesterol went up to 0.330 (110) mg. It returned to normal, however, within a fortnight.

#### THE CHOLESTEROL CONTENT OF FOODS

Data concerning the cholesterol content of the usual articles of food are extremely scarce, and so far as can be ascertained, no such determinations have been made by the Bloor method. For the sake of a fair comparison with the changes observed in the cholesterol percentage of the blood during any given diet it seemed important to establish the cholesterol percentage of the components of these diets by the same method by which the blood was tested. Table 2 shows the values found in samples of the food used during the diet experiments. It should be



TABLE 1.—BLOOD CHOLESTEROL OF THE WRITER, NOV. 23, 1914  
JUNE 16, 1916\*

DATE	AUTENRIETH (MG. CHOLESTEROL IN 5 C.C. CHLOROFORM)	BLOOR I (MG. CHOLESTEROL IN 5 C.C. CHLOROFORM)	BLOOR II (MG. CHOLESTEROL IN 5 C.C. CHLOROFORM)
Autenrieth-Hellige Colorimeter			
Nov. 23, 1915 . . . . .	0.180 (60)		
Jan. 31, 1916 . . . . .	..	0.216 (72)†	0.260 (86)
Feb. 1 . . . . .	..	0.272 (90)	0.300 (100)
Mar. 1 . . . . .	..	0.272 (90)	
9 . . . . .	..	0.272 (90)	
18 . . . . .	..	0.272 (90)	
25† . . . . .	..	0.330 (110)	
29 . . . . .	..	0.330 (110)	
Apr. 6 . . . . .	..	0.300 (100)	
9 . . . . .	..	0.272 (90)	
17 . . . . .	..		0.330 (110)
22 . . . . .	..	0.272 (90)	
June 16 . . . . .	..	0.272 (90)	
17 . . . . .	..	0.272 (90)	0.330 (110)
Duboscq Colorimeter			
17 . . . . .	..	0.275 (91)	0.333 (111)
18 . . . . .	..	0.272	0.333 (111)
19 . . . . .	..	0.272	0.330 (110)

\* The technic used for these tests is identical with that described in Luden's<sup>3</sup> data on the cholesterol content of the blood of goats, with the exception only that the Duboscq colorimeter set at 10 mm. and a standard test 0.400 mg. was used instead of the Autenrieth-Hellige instrument. It should be remembered also that all colorimetric estimations are influenced by the individual "color vision" of the operator, even when all other factors are identical; hence my "normal" cholesterol values which were found in a series of healthy persons read somewhat higher than the values quoted by Bloor.<sup>4</sup> It should be added that in a large series of tests run parallel with the Duboscq and the Autenrieth colorimeters the difference between the readings of the two instruments kept constant within the following range: Duboscq 0.222 (74), Autenrieth 0.216 (72); Duboscq 0.272 (91), Autenrieth 0.272 (92), the greatest difference being 0.008 (2). Consequently the cholesterol values obtained while the Autenrieth colorimeter was still in use, do not need any correction. Details concerning these parallel tests and of cholesterol values found in health and disease will be published shortly.

† Slight attack of appendicitis.

‡ Values in parentheses give milligrams of cholesterol per 100 c.c. of whole blood; the values in the test are milligrams per 0.5 c.c. of whole blood, or "test values."

remembered that a number of factors are bound to play an important part in the cholesterol value of foodstuffs. The breed, the age, and the mode of feeding animals will not be without influence on the cholesterol content of the food the animals supply. Even different parts of the meat of the same animal may have slightly different values. The time of calving materially affects the richness of the milk and its percentage of cholesterol, and in the case of cheese, for instance, the special brand and the ripening may not be without effect. Absolute data can, therefore, be obtained only by an extremely large number of determinations. The writer is fully aware of this, but has decided to record the experimental

findings in Table 2 for two reasons: First, the cholesterol content of the various articles of food used during the experiments must be closely associated with the results obtained; second, since present data on the subject are either vague (Rothschild,<sup>45</sup> for instance, states that eggs, cream, milk, and cheese are rich in lipoids, but gives no definite values) or obtained by older methods, it may be of general interest to know the approximate cholesterol percentage of at least a few of the common articles of food obtained by the Bloor method, allowance being made for slight variations in different samples of the same kind of food (Table 2).

TABLE 2.—CHOLESTEROL OF FOODS

Food	WRITER'S DETERMINATIONS DUBOSCQ COLORIMETER		OLDER METHODS <sup>41</sup> (PER CENT)	
	Bloor I (mg. cholesterol in 6 c.c. chloroform) mg. per 100 c.c.	Bloor II		
Yolk of egg, raw, 3 gm. §	2.660 (888)	2.660 (888)	2.15	1.75
Yolk of egg, hard boiled, 40 per cent water	2.660 (888)	2.660 (888)	..	..
Yolk of egg, desiccated	4.000 (1333)	4.000 (1333)	..	..
Milk, raw, 3 c.c.	0.080 (28)	0.080 (28)	..	..
Cream, raw, 3 c.c.	0.185 (61)	0.185 (61)	..	..
Butter, 3 gm.	0.472 (157)	0.880* (298)	0.190	
Butter-fat	..	..	0.200	0.220
Maize	..	..	0.100	
Mushrooms ( <i>Agaricus campestris</i> )	0.444 (148)	0.307 (102)	0.520†	
Mushrooms ( <i>Agaricus campestris</i> ) with sauce	0.210 (70)	0.181 (60)	..	..
Beef, raw, 3 gm.	0.160 (53)	0.160 (53)	..	..
Beef, roast	0.190 (63)	0.190 (63)	..	..
Beef, smoked, dried	0.181 (60)	0.250 (83)	..	..
Chicken, roasted, breast	0.380 (127)	0.380 (127)	..	..
Fish, black bass	0.250 (83)	0.250 (83)	..	..
Oatmeal	0.000† (0)	0.000† (0)	..	..

\* Bloor II tests appear to contain some kind of coloring material.

† *Boletus edulis*.

‡ Autenrieth method also negative.

§ Observe that egg yolk has roughly 10 times the value of normal blood.

In selecting the sample of fish, a very dry piece from the center near the spine was used and tested with blotting-paper to see that no trace of grease was present. The difference between the percentages for raw and roasted beef is explained by the loss of water that occurred in roasting. It is interesting to note that the different tests of the yolks of eggs correspond closely. The tests were made with a Duboscq colorimeter set at 10 mm. and the standard cholesterol solution containing 0.400 (133 mg. per 100 c.c.) mg. per 6 c.c. of chloroform used in our blood cholesterol determinations.

## INFLUENCE OF DIGESTION ON THE BLOOD CHOLESTEROL

Bloor<sup>2</sup> states that in dogs the process of digestion and the chemical constituents of the food do not influence the cholesterol content of blood to any appreciable extent. The effect of digestion in ruminant herbivora has been discussed in my work on the blood of goats. So far as could be ascertained no data have yet been published on the changes occurring in the blood cholesterol of normal persons during the digestion of the average mixed diet.

Three experiments were made to study the effect of the digestive process on the writer's cholesterol standard during the usual mixed diet. In every instance the first test was made before breakfast, as Bloor<sup>2</sup> has found that the postabsorptive period, eight to sixteen hours after the last meal, is "practically the only time when the blood is free from the influence of ingested or mobilized fat." According to Bloor and Rothschild, cholesterol and fat metabolism are closely associated. Whatever may be the exact time required for elimination of the other lipoids from the blood, the results obtained in these experiments seem to indicate that the blood cholesterol returns to its "standard value" in approximately four hours even when a considerable amount of food rich in cholesterol has been consumed. Consequently the time allowed—twelve hours—would be amply sufficient to exclude the effect of digestion from the first test. The subsequent tests were made at one hour's interval each, with the exception of the first test after the midday meal which had to be taken after two hours on account of the absence of those who took the blood. For each test 3 c.c. of blood were taken from the cubital vein by means of a graduated syringe fitted with a hypodermic needle, according to Bloor's method,<sup>3, 4</sup> the method used in all my experiments. The blood was boiled up immediately after it had been taken. It was found necessary to let a week elapse between the two experiments as the repeated introduction of the hypodermic needle caused the cubital veins—the left and right were used alternately—to collapse, small thrombi being formed which obstructed the lumina. Attempts to use the veins on the back of the hand gave unsatisfactory results, the caliber of most of these being too small, or, when sufficiently large, it was impossible to fix the vein itself and it slid aside when the needle was introduced.

The results shown in Table 3 were obtained in these experiments:

TABLE 3.—HOURLY TESTS OF CHOLESTEROL IN WRITER'S BLOOD DURING THE PROCESS OF DIGESTION

*First Experiment, Aug. 2, 1916*

Blood taken before breakfast showed a cholesterol value of 0.272 (90 mg.) by the Bloor I test and 0.333 (111 mg.) by the Bloor II test; that is, the usual interval between the two tests previously observed in the postabsorptive period.\*

## Breakfast (8 A. M.)

2 egg sandwiches (1 egg)

 $\frac{1}{2}$  cantaloupe

2 cups of tea (milk and sugar)

## DUBOSCQ COLORIMETER

Bloor I      Bloor II  
(mg. cholesterol in 6 c.c. chloroform)

Blood taken 1 hour after breakfast.....	0.347 (116)	0.420 (140)
" " 2 hours " " .....	0.333 (111)	0.380 (127)
" " 3 " " .....	0.280 (95)	0.350 (117)
" " 4 " " .....	0.272 (90)	0.330 (110)

## Dinner (12 M.)

1 cup cold broth

1 "tartar" steak (raw)

1 egg yolk

1 small slice of bread with butter

2 cups of coffee (cream and sugar)

Blood taken 2 hours after dinner.....	0.343 (114)	0.472 (157)
" " 3 " " .....	0.363 (121)	0.500 (167)
" " 4 " " .....	0.275 (91)	0.330 (110)

*Second Experiment, Aug. 7, 1916*

Blood taken before breakfast showed 0.272 (90) mg. cholesterol (Bloor I test) and 0.333 (111) mg. (Bloor II test).

## Breakfast (8 A. M.)

90 gm. raw beef

1 small slice of bread with butter

 $\frac{1}{2}$  cantaloupe

2 cups of coffee (sugar and cream)

DUBOSCQ  
COLORIMETERAUTENRIETH-HELLIGE  
COLORIMETER

Bloor I      Bloor II      Bloor I      Bloor II  
(mg. cholesterol in 6 c.c. chloroform)

Blood taken 1 hour after breakfast..	0.330 (110)	0.338 (129)	0.358 (119)	0.342 (114)
" " 2 hours " " .....	0.285 (95)	0.363 (121)	0.284 (95)	0.362 (121)
" " 3 " " .....	0.285 (95)	0.363 (121)	0.284 (95)	0.362 (121)
" " 4 " " .....	0.272 (90)	0.333 (111)	0.272 (110)	0.330 (110)

## Dinner (12 M.)

2 ham sandwiches

1 cottage cheese sandwich

1 egg sandwich ( $\frac{1}{2}$  egg)

2 cups of coffee (sugar and cream)

Blood taken 2 hours after dinner.....	0.307 (102)	0.363 (121)
" " 3 " " .....	0.272 (90)	0.333 (111)
" " 4 " " .....	0.272 (90)	0.333 (111)

*Third Experiment†*

Blood taken 4 hours after last meal showed 0.272 (90) mg. cholesterol (Bloor I test) and 0.333 mg. (Bloor II test).

## Light luncheon (4-5 P. M.)

3 small slices of bread with butter

2 cups of tea (moderate amount  
of sugar and cream)

Blood taken 1 hour after luncheon...	0.277 (92)	0.333 (111)
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\* The cause of the interval between the two tests has been discussed elsewhere by the writer.

† This experiment was made several times on different dates to determine whether patients could be allowed a light breakfast before their blood was tested.

As may be seen from the foregoing experiments, a light lunch consisting of bread with butter and tea or coffee does not appear to produce any marked changes in the blood cholesterol, or at any rate the changes have been eliminated within an hour. The tests made after the more substantial meals seem to show that the cholesterol content of the blood returns to its "normal standard" in approximately four hours even when as much as three-fourths of a pound of raw beef and the yolk of an egg have been consumed at one meal. This fact should be borne in mind in considering the results obtained from an exclusively meat diet. (See Table 5.)

#### EXPERIMENTS SHOWING THE EFFECT OF THE DIET ON THE CHOLESTEROL CONTENT AND THE CYTOLOGY OF THE BLOOD

The following experiments were suggested by the current belief that there is a causative relation between the increased consumption of meat and the incidence of cancer. Many writers do not hesitate to endorse this view. Williams writes: "I am persuaded that the ascertained facts justify the belief that there is a certain relation between the condition of nutrition and the incidence of cancer growth." Bulkley has repeatedly called attention to the influence of the diet on the course of malignant disease. Von Müller and von Bauer<sup>33</sup> in their clinical lectures both emphasized the fact that the increase of cancer in Bavaria might be due, in part at least, to increased consumption of meat among the Bavarian peasantry. Hoffman comes to similar conclusions from his cancer statistics.

Cytologic changes in the blood in malignant disease have been reported by Gruner, who based his work on the Arneth theory, and who succeeded, moreover, in reproducing these cytologic changes in his own blood by dietary measures.

Although some of Gruner's deductions may be open to criticism from a hematologic point of view, the main idea of his work and the honest effort which it embodied seemed to deserve recognition in a practical form; namely, the repetition of his experiment and the checking up of his results through independent investigation. Consequently certain of my experiments have been carried out along the lines suggested by him. Moreover, it seemed possible that experiments of this kind might furnish data concerning the influence of the diet on the lymphocytic reaction and on the cholesterol content of the blood and, therefore, in a wider sense, on the relation of metabolism to the cancer problem.

Gruner has adopted a very detailed classification for the morpho-

logic changes he observed in the leukocytes and lymphocytes of patients suffering from malignant conditions and in his own blood in dietetic experiments. Many of the pathologic nuclei he describes, however, somehow give the impression that they are perhaps artefacts due to accidents in staining or the mechanical effect of making the smear. Amitotic division, for instance, has been admitted for the lymphocytes and large mononuclears by Weidenreich; but some of Gruner's diagrams (for example, Figs. 21 and 23) suggest a folding rather than an actual division of the nucleus. Two of his varieties of atypical neutrophil leukocytes, however, seem above suspicion and have, therefore, been taken into account in my experiments inasmuch as no mechanical effect could produce the peculiar shape of their nuclei. These are the "ring-form" in which the nucleus is ring-like, and "bizarre forms" in which the nucleus represents a solid compact disc or bar which sometimes suggests the shape of the letter L or J.

Hematologists (Downey, Weidenreich) consider that the "ring-form" must be looked upon as an overlapping of the two ends of the nucleus since no true rings are found in human blood though they have been described in the blood of rats. They concede, nevertheless, that in perfect smears and in increased numbers these cells are striking enough to be worthy of consideration as supporting the Arneth theory.

Gruner claims that the "ringform is frequent in carcinoma," that "neutrophils with bizarre forms are characteristic for malignant conditions," that "a relative abundance of lymphocytes is not found in malignant disease," and that "one can produce the blood picture of carcinoma . . . by partaking of certain articles of food, notably pork and to a less extent, other red meats." These statements were corroborated in every respect by my experiments and were, moreover, illustrated in a striking manner by a case of inoperable carcinoma of the sigmoid that will be discussed later on.

My individual cholesterol standard having been established (Table 1), my individual lymphoid defense, its relation to the neutrophil count and the number of ringforms or bizarre forms present in my blood under ordinary conditions, remained to be determined. This was done by a number of differential counts. The blood smears were made before breakfast to eliminate the influence of digestive leukocytosis; 200 cells were counted from 3 smears on every occasion. The variations in the different counts were found to range from 29 to 31 per cent for the lymphoid defense and from 49 to 55 per cent for the neutrophils. The average number of atypical forms in the latter was 2 to 3 per cent of

ringforms and 2.5 to 3.5 per cent of bizarre forms. For three consecutive days preceding the experiment the relation was as follows: Lymphoid defense : neutrophils : : 80 : 54; ringforms : bizarre forms : :

TABLE 4.—THE EFFECT OF GRUNER'S DIET ON WRITER'S BLOOD CHOLESTEROL AND CYTOLOGY

Experiment 4, June 20-23, 1916

Gruner's diet: Milk and water, lettuce and toast; no butter, but jam *ad libitum*. Very little jam was used.

DAY	BLOOD CHOLESTEROL—DUBOSCQ COLORIMETER		LYMPHOID DEFENSE (Per Cent)	NORMAL NEUTROPHILS (Per Cent)	ATYPICAL NEUTROPHILS	
	Blood I (mg. cholesterol in 6 c.c. chloroform)	Blood II (mg. cholesterol in 6 c.c. chloroform)			Ringform (Per Cent)	Bizarre (Per Cent)
1	0.342 (114)	too brown to test	26	57	2.0	3
2	0.272 (91)	" " " "	30	54	1.0	3
3	0.186 (62)	" " " "	33	46	1.5	3

The slight initial increase observed in the blood cholesterol may have been due to the rather severe nature of the diet to which the body had to become accustomed. On the first day the writer was chronically hungry and had a severe headache in consequence, but during the two following days she felt perfectly well and comfortable. It is a well-known fact that fasting is always accompanied by an increase of the blood cholesterol (Rothschild).<sup>44</sup> The changes found in the cytology of the blood were still very slight, but the drop of the blood cholesterol to 0.186 mg. and the accompanying increase of lymphocytes and decrease of neutrophils is interesting when compared with the results of the subsequent experiments.

TABLE 5.—THE EFFECT OF AN EXCLUSIVE MEAT DIET ON WRITER'S BLOOD CHOLESTEROL AND CYTOLOGY

Experiment 5, June 24-July 1, 1916

Exclusive meat diet: Three thin slices of dry bread, 4 by 4 inches, had to be taken after the third day to help the meat down.

DAY	BLOOD CHOLESTEROL—DUBOSCQ COLORIMETER		LYMPHOID DEFENSE (Per Cent)	NORMAL NEUTROPHILS (Per Cent)	ATYPICAL NEUTROPHILS	
	Blood I (mg. cholesterol in 6 c.c. chloroform)	Blood II (mg. cholesterol in 6 c.c. chloroform)			Ringform (Per Cent)	Bizarre (Per Cent)
1	..	..	33	54.5	0.5	1.0
2	..	..	28	65.0	2.0	2.0
3	..	..	24	66.0	3.0	4.0
4	0.342 (114)	0.388 (129)	16	72.0	4.5	9.0
5	..	..	15	73.0	5.5	5.0
6	0.358 (119)	0.416 (139)	19	70.0	5.5	12.0
7	0.374* (124)	0.434 (144)	18	66.0	3.5	2.0
8	0.342 (114)	0.458 (153)	17	72.0	9.0	8.5

\* Diarrhea.

The results obtained by the all-meat diet seem worthy of consideration for several reasons. The changes observed in the cytology and in the cholesterol content of the blood are too marked and too gradual to be explained by mere coincidence. The increase in the blood cholesterol from 0.186 (62) mg. to 0.372 (124) mg. cannot be attributed to the effects of hunger because very considerable quantities of meat were consumed at each meal. It is to be regretted that at first the exact amount was not determined by weight, but it may suffice to state that the writer conscientiously tried to eat as much meat as she possibly could for breakfast, luncheon, and dinner, a smaller quantity being ingested at 4 P. M. It was subsequently found that the average amount of meat consumed daily had been from  $1\frac{1}{4}$  to  $1\frac{1}{2}$  pounds. Coffee and tea were taken as usual, but no alcohol, since it is never used. The exclusive meat diet was not accompanied by any unpleasant symptoms whatsoever, although it was found necessary to allow a very small quantity of dry bread after the third day, since meat in hot weather—the experiment was made between June 23 and July 1—loses its attractions as a steady diet. No sensation of hunger was experienced between meals as in the previous experiment, and perfect health as well as unhampered mental activity were enjoyed throughout.\* On the seventh day, at the beginning of which the highest cholesterol value was registered, there was a slight attack of diarrhea. On the following day peristalsis was normal again, but the blood cholesterol had dropped to 0.342 (114) mg. Since the elimination of cholesterol by the feces is one of the means by which the cholesterol balance is preserved (McNee), it seems logical to assume that the body resorted to increased peristalsis in order to maintain its equilibrium of health. The fact that the same automatic regulation of the cholesterol balance was observed also in a later experiment would seem to support this view, and will be more fully discussed in connection with Experiment 7.

The gradual but steady drop in the lymphoid defense from 33 to 17 per cent, the parallel increase of the polymorphoneutrophils from 46 to 72 per cent, and the unusual number of atypical neutrophils—9 per cent ringforms, 12 per cent bizarre—which appeared in the blood as the cholesterol percentage reached its highest values, suggest a very definite relation between the chemical composition and the cytology of the blood,

\* Because of its bearing on these experiments I might add that the Union Central Life Insurance Company reported most favorably on the results of their medical examination made at this time.



while the changes observed in both appear to be closely associated with the chemical nature of the food consumed. The same observations could be made in every one of my experiments.

The cytologic changes found in the blood during the exclusive diet are, moreover, in perfect accordance with Gruner's findings, which they corroborate. The two points on which he lays particular stress regarding the similarity between the blood picture during excessive meat consumption and in carcinoma—reduction of the lymphocytes and the appearance of atypical neutrophils in markedly increased numbers—seem to be borne out also by the following observations:

TABLE 6.—OBSERVATIONS A AND B

SUBJECT	BLOOD CHOLESTEROL—DUBOSQ COLORIMETER		LYMPHOID DEFENSE (Per Cent)	NEUTROPHIL COUNT (Per Cent)	ATYPICAL NEUTROPHILS—RINGFORMS (Per Cent)
	Blood I (mg. cholesterol in 6 c.c. chloroform)	Blood II (mg. cholesterol in 6 c.c. chloroform)			
A. Dr. F.: Inoperable carcinoma of sigmoid	0.416 (139)	0.416 (139)	11	70	10
B. Man in perfect health, who had tropical malaria sixteen years previously	0.462 (154)	0.472 (157)	40	50	2

It is noteworthy that whereas the blood cholesterol of the healthy person is slightly higher than that of the carcinomatous patient, the unusually high lymphoid defense, 40 per cent, and the small percentage of ringforms, 2 per cent, of the former are in striking contrast to the unusually low lymphoid defense, only 11 per cent, and the high percentage of atypical neutrophils, 10 per cent, of the latter.

TABLE 7.—OBSERVATIONS C AND D

SUBJECT	BLOOD CHOLESTEROL DUBOSQ COLORIMETER		LYMPHOID DEFENSE (Per Cent)	NEUTROPHIL COUNT (Per Cent)	ATYPICAL NEUTROPHILS	
	Blood I (mg. cholesterol in 6 c.c. chloroform)	Blood II (mg. cholesterol in 6 c.c. chloroform)			Ringforms (Per Cent)	Ringforms (Per Cent)
C. Dr. F. after colostomy	0.330 (110)	0.374 (124)	21.5	67.0	3.0	7
D. Dr. F. after radium treatment	0.240 (80)	0.260 (86)	33.0	62.5	3.5	0

The relation between the blood cholesterol and the blood cytology is further illustrated by the changes produced in the blood of the same

omatous patient, Dr. F., by radium therapy, which temporarily cured the disease if it did not cure it, and caused a marked improvement in the general condition.

During the following months the lymphoid defense of the patient fell again to 16 per cent, which seems in accordance with the view expressed by the patient's physician, Dr. Howard Kelly, that "a permanent cure was not to be expected." It is greatly to be regretted that blood cholesterol could not be tested again, since there is every reason to assume that a renewed increase in the blood cholesterol would have corroborated previous observations. Although at present definite conclusions would be premature, there seems little doubt that further investigations of the relation between the chemistry and the cytology of the blood may prove to be of great value in the study of malignant conditions. In the meantime the explanation seems admissible that a high lymphoid defense is effective in maintaining the normal equilibrium even in the presence of high cholesterol values, although other factors, elimination of cholesterol by the feces, for instance, may be equally important. Levy and Rowntree have shown that the balance of health, that is, the chemical balance of the body, swings between extremely narrow limits. The acidity of 'acidosis' and the alkalinity of 'alkalosis' may be compared with perfect scientific accuracy to the 'acidity' of distilled water and the alkalinity of certain varieties of tapwater" (Rowntree). Consequently, any factors by which the normal equilibrium might be disturbed are worthy of consideration. The cholesterol content of the blood as well as the lymphoid defense would appear to be factors of no small importance.

#### VEGETABLE DIET

The diet used in this experiment consisted of vegetables, fruit, and dry bread or toast. No butter was used except such as had been added to the vegetables in cooking, and since the latter were not very "rich"—never creamed for instance—the amount of butter consumed can be safely considered very small. The vegetables consisted of carrots, cauliflower, string beans, asparagus, boiled or mashed potatoes, spinach, lettuce, and cucumbers. In a few instances, mushrooms were not avoided, but the steady decrease of the blood cholesterol (below normal) would tend to show that their consumption did not seriously interfere with the results of the experiment even though their cholesterol content is relatively high. No fish and no meat in any form were partaken of

during the time of experimentation. Coffee and tea were drunk as usual but no alcohol in any form. It would seem that the diet was entirely sufficient to meet the requirements of the body, for the duration of the experiment at least, since no sensation of hunger between meals was experienced and no loss of weight could be observed. Peristalsis was absolutely normal and the writer felt extremely well and "fit" throughout the experiment.

TABLE 8.—THE EFFECT OF A VEGETABLE DIET ON WRITER'S BLOOD CHOLESTEROL AND CYTOLOGY

*Experiment 6, Aug. 2 to 12, 1916*

DAY	BLOOD CHOLESTEROL DUBOSCQ COLORIMETER (mg. cholesterol in 6 c.c. chloroform)		LYMPHOID DEFENSE	NEUTROPHIL COUNT	ATYPICAL NEUTROPHILS	
					Ringform	Barre
1			17	71	3.5	3.0
2	0.312 (104)	0.386 (128)	28	65	0.0	3.0
3						
4	0.302 (100)	0.358 (119)	21	70	0.5	3.5
5			33	58	1.0	1.5
6	0.202 (67)	0.312 (104)	28	60	2.5	0.5
7						
8	0.242 (80)	0.312 (104)	30	61	1.5	0.5
9	0.242 (80)	0.302 (100)	29	62	1.0	2.0
10	0.242 (80)	0.302 (100)	33	57	0.5	3.0

The results obtained by the vegetable and fruit diet present a contrast as well as a complement to those of the exclusive meat diet. Whereas the blood cholesterol slowly but steadily decreased from 0.342 mg. to 0.202 mg. on the fifth day and finally seemed to settle down to a new standard, 0.242 mg., which was found on three consecutive days, the lymphoid defense increased from 17 per cent to 33 per cent, with a parallel drop in the neutrophils and a marked reduction of the number of atypical cells.

In order to give the body sufficient time to swing back to normal values, and because of the tendency to collapse shown by the cubital veins, described above, eleven days were allowed to elapse before another blood test was made. During this interval the usual mixed diet was used again. The following values were found at its close:

TABLE 9

BLOOD CHOLESTEROL DUBOSCQ COLORIMETER		LYMPHOID DEFENSE	NEUTROPHIL COUNT	ATYPICAL NEUTROPHILS	
Blood I	Blood II			Ringform	Barre
(mg. cholesterol in 6 c.c. chloroform)		Per Cent	Per Cent	Per Cent	Per Cent
0.266 (89)	0.307 (102)	31	62	0.5	3

Apart from the very slight increase in the neutrophil count, the normal standard had been reached again. The difference between the original cholesterol standard, 0.272 (90) mg., and the last reading, 0.266 (89) mg., that is, 0.006 (1) mg., can hardly be considered significant. The intimate relation between the chemistry and the cytology of the blood and the diet, previously observed, seems to be confirmed by this experiment.

#### INFLUENCE OF AN EXCESS OF CARBOHYDRATES ON THE CHOLESTEROL CONTENT AND THE CYTOLOGY OF THE BLOOD

Two seemingly unrelated problems formed the basis of this experiment; namely, the cause of the epithelial proliferation on the tongues of rats observed by Stahr<sup>55</sup> after exclusive feeding of oats, and the ability of the body cells to synthesize cholesterol from cholesterol-free substances, defended by Dezani.<sup>12, 13</sup> The practical importance of these problems and their possible relation to each other is such that a brief outline of the work referred to may be of value.

Stahr found that epithelial tumors of considerable size on the tongue originating without exception from the papillæ circumvalate could be produced in a great number of rats of different species by feeding the animals exclusively with oats. No other diet resulted in this tumor formation. Congenital tumors were never observed, although as many as seven generations of the same family were used in the experiment. The best results were obtained when the animals were fed on oats continually and almost exclusively ("dauernd und fast ausschliesslich") as soon as they had been weaned. In very old rats the excessive oat diet did not seem to cause any epithelial proliferation, while adult rats, that is, full grown but not old animals, seemed to respond to the irritant in varying degrees. Stahr attributes his results, in part at least, to chronic irritation produced by the oat husks which were found embedded in the tongues of the animals in which tumors occurred. Nevertheless, he admits that a number of wild rats in whose tongues the sharp pointed husks were also found embedded showed no trace of tumor formation. The time required for the lesions to become manifest and their respective size varied considerably in different animals. A great number of the larger tumors developed in from five to seven months, the initial stages being visible in about four weeks to two months. In many instances, however, the tumors grew so slowly that there seemed to be no visible increase after five months. Stahr considers that this divergence can be

accounted for only by the fact that the rats were not endowed with same degree of predisposition ("dass die Ratten eben verschieden disponiert waren"), a conclusion which will readily be admitted. He adds that our conception of the nature of this so-called "disposition konstitution," which has been somewhat vague for many years, will become clear and definite as a result of recent investigations. The accuracy of the latter statement seems questionable. That the mechanical factors which he enumerates—anatomic formation of the mouth and motility of the tongue, either of which impeded or promoted the removal of the implanted husks, the nature of the irritant itself and the length of time the irritation was kept up—played an important part in the process of atypical proliferation cannot be doubted, but there are other factors the significance of which should not be underrated; namely, the chemical composition of the oat diet and the power of elimination of the individual rat. Notwithstanding the masterly analysis of causes found in his report, Stahr does not seem to take these factors into consideration, for the internal causes (innere Ursachen) which he discusses at great length are of an entirely different character. That both the "disposition and constitution" to which he refers, however, are intimately associated with the ability of the individual organism to eliminate or metabolize certain articles of food, will, I think, be readily conceded. Many of the problems of individual metabolism have by no means been solved as yet.

In discussing the nature of the growths produced by the oat diet, Stahr states that they represent "at least the earliest evidence of an epithelial tumor, of a true blastoma"<sup>55</sup> (p. 225). He discusses the relation between harmless proliferation and malignant hyperplasia at great length and comes to the conclusion that in the initial stages it is impossible to decide whether any given type of atypical epithelial proliferation is destined to retain its benign character or to develop into a true carcinoma, "so that consideration must be taken of internal causes which affect these originally benign growths in such a way that they discard normal bounds and develop into cancer." The context shows that Stahr evidently looks for the "internal causes" within the tumor cells themselves, inasmuch as he defends the hypothesis that in malignant conditions new types of cells are formed in circumscribed areas, and lawless proliferation is an inherent characteristic of these newly formed cells. In other words, the tumor cells as such are responsible for their onslaught on the welfare of the body. Would it not be equally reasonable to assume

that lawless proliferation is the manifestation of "internal causes" in another sense; that is, that some substance stimulating cell proliferation is supplied by the body itself through faulty metabolism, and that the atypical character of these proliferating cells is merely the result of an overhastened rate of cell-production under the influence of this constantly applied stimulant? We know that in hyperthyroidism, for instance, a toxic substance is constantly produced which goads the heart into lawless activity, and that infinitesimal doses of this substance, Kendall's<sup>28</sup> alpha-iodin compound, similarly increase the heart rate of normal animals for a short time. This has been demonstrated experimentally. It has also been found that the normal heart swings back to its usual rate of action as soon as the toxic compound has been either eliminated or destroyed by normal metabolism. We admit the "unripe" character of the so-called malignant cells and we know that the more embryonic or unfinished the cells of a tumor are, the more rapid and destructive its growth. Would it not be reasonable to deduce from the foregoing facts that substances supplied in the food and insufficiently metabolized by inadequate organs could become the cause of lawless cell proliferation, inasmuch as the daily intake of food would furnish a constant stimulant that might bring about the hurried coinage of unfinished, atypical cells, embryonic in character, simply because the rate of production did not allow them time to become full-grown? It is well known that under suitable conditions normal cells can be transplanted and made to grow *in vitro* (Foote<sup>16</sup> and Burrows). The origin of metastatic tumors can be traced in many instances to strands of single cells that have been crowded out by the rapid growth of the mother tumor, and the danger of scattering and implanting stray tumor cells in operative procedures is recognized by surgeons. These observations, as well as many others that cannot all be enumerated here, seem to support the view that the body itself furnishes the conditions by which proliferation is either regulated and kept within normal bounds or incited to become lawless and destructive. That the invasive growth of tumor cells ("infiltratives Wachstum," Joest and Ernesti) might be interpreted as merely the result of the increased rate of production referred to above, does not seem inadmissible.

The fact that the majority of the oat-fed rats developed tumors, the striking absence of tumors in animals fed on other food, and the presence of oat husks in the tongues of wild rats that showed no tendency to tumor formation (proving that the irritant alone was insufficient to

produce the lesions) would seem to indicate that the diet itself and way in which the animal was able to handle it, may have been prime factors in the results obtained by Stahr. The chemical analysis of blood of these tumor rats and the study of their blood cytology undoubtedly have furnished valuable data concerning the effect of diet on the development of the tumors.

The synthesis of cholesterol by the body cells from substances containing only the elements carbon, hydrogen, and oxygen, of which the cholesterol molecule,  $C_{27}H_{46}O$ , is composed, has been a subject of much controversy. Bloor<sup>6</sup> (page 581) makes the guarded statement that together with other lipoids, cholesterol is "probably" synthesized by the animal organism, whereas Rothschild<sup>41</sup> (page 233) boldly asserts that "there is no synthesis of cholesterol in the body." In discussing the question, Bloor calls attention to the work of Dezani,<sup>12, 13</sup> Gardner and Lander. While the experiments of Gardner and Lander furnish a striking illustration of the power possessed by the animal organism to transform cholesterol into body cells or, at any rate, to utilize it for the purpose of cell formation, the term "synthesis" would hardly seem applicable to the process they studied; that is, the gradual development of the chick embryo from the egg. Synthesis may be defined as "the artificial building up of a chemical compound by union of its elements." Since the egg already contains a high percentage of cholesterol, the growing chick does not need to effect the union of the elements but merely convert the substance into cells. Moreover, "the fully developed chick contains only as much cholesterol as the egg did before hatching" (Rothschild, p. 230).

Dezani's work, on the other hand, seems far more suited to demonstrate a true synthesis of cholesterol, as a brief abstract of his original report will show. Having established the average weight and the average total cholesterol content of a certain breed of mice, he divided the sixteen remaining animals into groups of four. These animals were fed for twenty-three days on a mixture of casein and maize from which all the cholesterol had been extracted for a week with ether-alcohol. In addition, Group I received a certain amount of mineral salts, Group II mineral salts and lecithin, Group III mineral salts and fat in the form of fatty acids and glycerin, and Group IV mineral salts, lecithin, and fat in the same form. The mice devoured this food greedily and seemed to thrive on it. Young growing mice had been chosen for the experiment. They gained in weight, developed normally, and seemed in perfect health.

At the end of seventeen days, however, they began to dislike the food and lost slightly in weight. Their coats became rough, but they were lively and the ears showed no sign of anemia. On the twenty-third day three of the mice were found dead in their cage and the rest were killed. The total cholesterol of each group was then determined by desiccating the bodies *in toto* and extracting the cholesterol by means of a special procedure devised by Dezani. Though no cholesterol had been supplied in the food, chemical analysis had shown that cholesterol had been daily eliminated by the feces, and the postmortem determinations proved that the total average cholesterol had been increased by about one-third in each group. The mice had been weighed in groups, and every group exceeded its initial weight, whereas a slight loss of weight which occurred during the last days of the experiment did not exceed 0.8 per cent of the total gain. Dezani considers, therefore, that the destruction of body cells alone cannot account for the marked increase of the total cholesterol, though it may have added slightly to the values, and that the animals must have synthesized the greater part of the surplus cholesterol from the cholesterol-free food on which they had been fed. He suggests the following explanation:

Under ordinary circumstances the body does not synthesize cholesterol, the amount essential to health being easily obtained "ready-made" in the food. Under special conditions, however, when no cholesterol is available, synthesis is resorted to by the body as an extreme measure in preference to the alternative of a cholesterol deficit. In other words, the body can synthesize cholesterol under the stress of necessity just as the heart can use all its reserve power when occasion demands. The organism soon tires of the unwonted effect, however, and loss of health, or decompensation results in the end, as was the case with Dezani's mice.

The question suggested by Stahr's experiment is the following: Could the results obtained have been due to a reduction of the lymphoid defense with parallel increase of the blood cholesterol in those animals which responded to the excessive oat diet by tumor formation? The relation between the blood cholesterol, the lymphoid defense, and the diet observed in the writer's experiments and the part played by cholesterol in cell proliferation both in normal growth and in the growth of tumors (Robertson and Burnett), justify this supposition, especially as Stahr's report contains no reference to the blood cytology or blood chemistry of his animals.

No data being available in regard to the cholesterol content of oats,



and the only chemical analysis of any kind of grain recorded being that of maize with 0.10 per cent of cholesterol (Table 1), it was decided to make a test by the Bloor method of the broken oats sold under the name of "Scotch oatmeal."\* This test was entirely negative. A second test was made according to the Autenrieth method on the assumption that the Bloor test might not be effective in dissociating certain chemical compounds in which the cholesterol in oats might be bound up, though as Mueller<sup>35</sup> has pointed out, Bloor's method of extraction "will be found to be practically complete" in other substances. By Autenrieth's method the substance to be tested is boiled for two hours with 25 per cent potassium hydroxid, and the combined action of strong alkali and boiling could reasonably be expected to effect the necessary dissociation if any cholesterol were contained in the oats in compound form. However, the results of this test were negative also. Since, then, no cholesterol appeared to be contained in oats, and Dezani's work suggested that even cholesterol-free food can cause an increase of the total cholesterol content of the body by synthesis of cholesterol, it still seemed possible that Stahr's rats had synthesized their cholesterol from the cholesterol-free oats. This surmise did not seem unreasonable because, as they are carbohydrates, oats contain the very elements, carbon, hydrogen, and oxygen, of which the cholesterol molecule is composed.

In order to verify this supposition a diet consisting as exclusively as possible of broken oats (Scotch oatmeal) was decided upon. Such a diet, even though the husks had been removed from the grain, would contain practically the same chemical compounds as the oats on which Stahr's rats had been fed. The chemical effects of the diet on the cholesterol content and the cytology of the blood being the chief object of investigation, the absence of the oat husks did not seem of great practical importance. That no vitamins were lost by the removal of the oat husks would seem to be demonstrated by Fig. 193, which shows that the oat grains were practically intact and surrounded by a slightly hairy capsule, thus being comparable to thrashed but unpolished rice.

Although for reasons to be discussed later, this experiment did not furnish conclusive data concerning the synthesis of cholesterol in the body, the results obtained may be of value inasmuch as they again confirm previous observations regarding the intimate relation between the diet, the lymphoid defense, and the cholesterol content of the blood.

\* Scotch oatmeal consists entirely of broken oats, and should not be confounded with the so-called "rolled oats."

Rothschild<sup>44</sup> has pointed out that the cholesterol content of the blood is increased by starvation, cholesterol being liberated from the body fat in which it is stored. Loss of weight was, therefore, to be studiously avoided during the oatmeal diet. It might be argued that the maintenance of the original body weight and especially an increase thereof in the course of the experiment would be ample proof that any rise in the blood cholesterol could not be attributed to the destruction of body tissues. However, Dezani's<sup>12</sup> first experiment had shown that the body will make every effort within its power to maintain its cholesterol balance even during starvation, and that a loss of 41 per cent of body weight is accompanied by a loss of only 15 per cent of the total cholesterol. Consequently, it seemed safer not to depend on the evidence of body weight alone, but to base the experiment on a strict maintenance of the metabolic balance in general. The following standards were therefore established:

1. The diet must consist of ground oats (Scotch oatmeal) as exclusively as possible.
2. It must contain all the elements needed to maintain the metabolic balance; namely, the requisite number of calories, the relative amounts of protein, fat, and carbohydrates.
3. The food requirements, compiled from Friedenwald and Ruhräh's (pp. 48-79) data corresponding to the age, sex and occupation of the experimenter, must be met, if necessary, by additional foodstuffs containing as little cholesterol as possible.

According to Voit, Rubner, Tigerstedt, Atwater and Benedict, quoted by Ruhräh<sup>18</sup> (pp. 51-54), the daily food requirements of the male adult doing light and moderately light work are as follows:

TABLE 10

	CALORIES	PROTEIN GM.	FAT GM.	CARBO- HYDRATES GM.
Voit: Physician at moderate work.....	2,833	127	89	362
Rubner: Male adult at moderate work....	2,600	..	..	..
Tigerstedt: Shoemaker at moderate work..	2,001-2,400	..	..	..
Atwater: German physician.....	2,680	131	95	327
Japanese professor.....	2,380	123	21	416

Friedenwald and Ruhräh<sup>18</sup> (p. 69) suggest the following standard:

For light work, 17 calories per pound of body weight.

For moderate work, 20 calories per pound of body weight.

They state further (pp. 55, 56) that "curiously enough, mental work does not apparently utilize heat or energy in the ordinary way. . . . In a respiration calorimeter, hard mental work; that is, the working out of abstruse mathematical problems requiring hours of time, does not cause any difference in registration. The same apparatus, however, sufficiently sensitive to register the heat generated by turning over a bed or by raising an arm." In discussing the relation of sex and body weight to food values required, they state<sup>18</sup> (p. 57): "On an average women are only about four-fifths as large as men, and consequently their dietarys for groups of women will require four-fifths the amount of food."

In consideration of these data and since carbohydrates were to form the chief component of the oatmeal diet, the food requirement of the Japanese professor given by Atwater, divided by four-fifths, were used as the basis for the oatmeal experiment.

TABLE 11

EXPERIMENTER	OCCUPATION	CALORIES	FOOD REQUIREMENTS		
			Protein Gm.	Fat Gm.	Carbohydrates Gm.
Forty years old; weight, 134.5 pounds . . . . .	Laboratory research; mental, light manual	2,000	100	30	325

The amount of fat was increased somewhat because the climate was rigorous, the experiment being made at the beginning of the cold season between October 26 and November 1, and because a liberal margin of fat in the diet might also guard against the combustion of the body fat. Moreover, the values quoted above would coincide satisfactorily with Ruhräh's estimate of the food requirements of a woman weighing 134.5 pounds at light work—17 (calories per pound of body weight, man at light work)  $\times$  134.5 (pounds body weight)  $\div$   $\frac{4}{5}$ —and the relative caloric values given by him for protein, fat and carbohydrates:

TABLE 12

1 gram protein	= 4 calories	100 grams protein	= 400 calories
1 " fat	= 9 "	30 " fat	= 270 "
1 " carbohydrates	= 4 "	332 " carbohydrates	= 1328 "
Total . . . . .			1998 "

From the figures given by Friedenwald and Ruhräh<sup>18</sup> (p. 49, the

fuel value of oatmeal and its relative percentage of protein, fat, and carbohydrates may be calculated as follows:

TABLE 13

	CALORIES	PROTEIN	FAT	CARBOHYDRATES
Oatmeal (raw) one pound	1800*	67 gm. (15 per cent)	22 gm. (5 per cent)	360 gm. (80 per cent)

\* Rolled oats = 1850.

Consequently the consumption of one pound of oatmeal would almost suffice to meet the food requirements, the slight deficit in the calories and protein being easily balanced by the addition of a small amount of other food with low cholesterol content, while the surplus of carbohydrates (28 gm.) contained in the oatmeal made up the deficit in fat (2.5 gm. of carbohydrate being equivalent to 1 gm. of fat).

An unexpected difficulty presented itself, however, in the process of cooking: owing to the amount of water absorbed by the cereal, the original bulk of oatmeal increases no less than four times. As a result, the consumption of a whole pound of oatmeal in its magnified form proved to be a physical impossibility, defying the most determined efforts. A compromise had to be resorted to and the following diet was adopted:

TABLE 14

	CALORIES	PROTEIN Gm.	FAT Gm.	CARBOHYDRATES Gm.
Oatmeal, $\frac{3}{4}$ pound (raw weight).....	1200	48	16	240
Oranges, 3.....	180	0	0	18
Milk, 2 glasses.....	320	14	24	30
Sugar, $\frac{1}{4}$ pound.....	450	0	0	112
Dried beef, $\frac{1}{8}$ pound.....	66	16	3	0
	2216	78	33	400

In this combination the total minimum requirement in calories was slightly exceeded, while the carbohydrate surplus of 100 gm. amply made up for the protein deficit of 22 gm., since, according to Rubner, 232 gm. of carbohydrates represent a fuel value equivalent to 211 gm. of protein. The diet seemed to guarantee a perfect maintenance of the metabolic balance, whereas the amount of cholesterol contained in 2 glasses of milk and  $\frac{1}{8}$  lb. of dried beef (the latter chosen on account of the salts and relatively small bulk) was far below that provided in eggs, butter, and meat during the ordinary mixed diet. (Milk 0.080 mg. cholesterol; dried beef 0.181 mg. cholesterol.) (Table 12.)

The following results were obtained on the six days of oatmeal diet. Within three days the blood cholesterol rose from 0.266 mg. to 0.400 mg. simultaneously the lymphoid defense dropped from 31 to 24 per cent (Table 15). As in previous experiments, the cytology of the blood in pace with these changes, for as the blood cholesterol reached its maximum and the lymphoid defense its minimum, the ringform and bizarre form of neutrophil leukocytes increased from 2 and 3 per cent respectively to 8 and 12 per cent.\* A steady increase in weight accompanied the above changes, showing that they were in no wise due to insufficient nutrition. On the fifth day of the experiment there was a sudden rise in the lymphocyte count from 24 to 31 per cent, preceded by a peculiar sharp pain in the left side the day before. This pain was confined to the region of the spleen. It differed from the pain caused by flatulence inasmuch as starting at 4 o'clock P. M., it never shifted or abated until about 11.30 P. M. when the experimenter fell asleep. During the two following days the splenic region remained very sore but the pain was no longer acute. The fact that the sudden increase in the lymphocyte count was preceded by pain in the region of the spleen suggests that the increased activity of that organ may have been accompanied by a certain amount of swelling. The pain itself was caused in all probability by adhesions around the spleen due to attacks of "Dutch malaria" from which the writer suffered for several years, but of which no recurrence had been observed during the past six years.

The delicate and automatic self-adjustment by which the normal balance is regulated in health is again illustrated by this experiment. After the blood cholesterol had reached the maximum of 0.420 (140 mg.) the lymphocytic reaction alone seems to have been unable to restore the balance and the blood cholesterol was again reduced by increased peristalsis as in the "all meat" diet. The cause of the increased peristalsis will be considered in the discussion. As soon as the ordinary mixed diet

\* It will be remembered that all the data, blood counts, cholesterol values, and weights were taken before breakfast throughout these experiments and that consequently diarrhoea and leukocytosis can be eliminated as a cause of the sudden change in the lymphocyte count.

† "Dutch malaria" is clinically known as recurrent fever. The cause of the illness, the *Spirillum obermeieri*, was found in the writer's blood at the time. Although the disease can be differentiated bacteriologically from other types of malaria, the subjective symptoms are practically identical. The spleen and the liver are often found enlarged, but these findings are by no means constant, and they did not occur in the writer's case. During one attack, however, a severe throbbing pain was felt in the splenic region and lasted for several weeks. This may have been caused by perisplenitis or by a splenic abscess. Since in the absence of a marked enlargement of the spleen neither of these conditions can be diagnosed with certainty in the living, the autopsy report alone can give conclusive evidence.

TABLE 13. THE EFFECT OF AN ANOMALOUS  
Experiment 7, Oct. 27 to Nov. 8, 1916

Day	Date	Food	Weight (Lbs.)	Blood Cholesterol Ducoco Colorimeter		Lym- phoid De- crease (Per Cent)	Normal Neutro- phils (Per Cent)	Atypical Neutrophils		Remarks
				Blood I (mg. cholesterol in 6 c.c. chloroform)	Blood II			Ring- form (Per Cent)	Bizarre (Per Cent)	
1	Oct. 27	Oatmeal diet	134.5	0.266 (89)§	0.347 (116)	31.0	61.0	3.0	4.0	Mixed diet since August; blood taken before break- fast.
2	28	" "	135.0	0.333 (111)	0.363 (121)	32.5	54.5	5.5	4.0	Slight discomfort from flatulence; bowels regular.
3	29	" "	135.0	" "	" "	" "	" "	" "	" "	Much discomfort from flatulence, otherwise well.
4	30	" "	135.5	0.400 (133)	0.420 (140)	24.0	65.5	6.5	5.0	Bowels regular, but stool deep yellow; no diarrhea. Flatulence very pronounced from 4 p. m. till asleep, 11 p. m.; pain in spleen;* bowels and stool like day before.
5	31	" "	136.0	0.400 (133)	0.420 (140)	31.0	62.0	6.0	5.0	Flatulence pronounced from 4 p. m. on; spleen region sore; slight diarrhea.
6	Nov. 1	" "	136.0	0.233 (78)	0.285 (98)	26.5	62.5	6.0	7.0	Flatulence from 4 p. m. very pronounced; spleen pain slight; slight diarrhea.
1	2†	Mixed diet	136.5	0.200 (67)	0.266 (89)	31.0	58.0	3.5	3.0	No flatulence; bowels regular; stool deep yellow; no spleen pain; fagged; otherwise well.
2	3	" "	136.0	0.266 (89)	0.333 (111)	36.0	57.0	1.5	2.0	Feeling very well; no flatulence; bowels regular.
3	4	" "	135.5	0.295 (98)	0.420 (140)	27.0	62.0	5.0	2.5	Very well; bowels regular; stools deep yellow.
4	5	" "	135.0	0.347 (116)	0.420 (140)	26.0	64	" "	" "	Feeling very well but slight diarrhea.
5	6	" "	134.5	0.266 (89)	0.380 (127)	30.0	55	" "	" "	Feeling very well; bowels regular; stools normal.
6	7	" "	134.5	0.266 (89)	0.350 (117)	30.0	53	" "	" "	Feeling well; bowels regular; stools normal.
7	8	" "	134.5	0.266 (89)	0.350 (117)	30.0	53	" "	" "	Feeling well; bowels regular; stools normal.

\* The pain in the region of the spleen did not abate at all, thereby proving that it was not gas pain due to flatulence, as seemed probable at first. The possible origin of this pain is considered in the discussion of the experiment.

† From Nov. 1 to 2 only ½ pound of oatmeal and ¼ pound of sugar were consumed, owing to the fact that the writer attended a dinner party. The low value of the blood cholesterol on the following morning was probably due to increased peristalsis during the previous day, and seems to indicate that the small amount of meat eaten at the party was not sufficient to increase the cholesterol value.

‡ Slides thrown away by mistake so that the average could not be established as on the preceding days by counts made by three different workers whose results tallied with only very slight differences.

§ Mm. per 100 c.c. of whole blood.

was used the increase in weight, from 134.5 pounds to 136.5 pounds, also disappeared, and the normal weight, 134.5 pounds, which had been constant for several years, was again registered within six days. The gradual loss of weight increase was accompanied by a slight rise of the blood cholesterol (0.266 (89) mg., 0.295 (98) mg., 0.347 (116) mg.) showing that, although the increase in weight may have been due in part to the absorption of water from the oatmeal diet by the tissues, a certain amount of fat had also been produced, as reduction of fat was accompanied by a rise in the blood cholesterol (Aschoff, Rothschild). After the fifth and sixth days, the normal cholesterol value, 0.266 mg., remained constant. The lymphoid defense was still slightly below the figure observed at the beginning of the experiment, but the number of atypical neutrophils, ringforms and bizarre forms had returned to 2.5 and 3 per cent respectively.

At the time of writing, Dec. 30, 1916, the blood cholesterol, lymphoid defense, atypical neutrophils and weight are as follows, the oatmeal diet having been eaten since the end of the experiment: Blood cholesterol, 0.275 mg.; lymphoid defense, 32 per cent; atypical neutrophils, ringforms, 1.5 per cent; bizarre forms, 2.5 per cent; weight, 135 pounds. These figures seem to support the deduction that, under normal conditions, there is a constant relation between the above named factors.

### DISCUSSION

Whereas the influence of the diet on the blood cholesterol and the cytology of the blood seems sufficiently clear in our experiments to require no further comment, three other points must be briefly discussed, namely, the cause of the increase in the blood cholesterol during the oatmeal diet which contained less cholesterol than the ordinary mixed diet, the cause of the slight attacks of diarrhea which occurred whenever the cholesterol values reached their maximum, and the significance of the atypical neutrophils.

It has already been stated that the increase of the blood cholesterol in the oatmeal experiment did not furnish conclusive evidence as regards the synthesis of cholesterol from cholesterol-free food, even though Dezan's work seemed to prove that cholesterol can be synthesized under special conditions. The lack of definite proof in our case may be readily explained by the fact that the methods used by Dezan for the determination of the total cholesterol of his mice could not be applied in the writer's work, for obvious reasons. As the increase of the cholesterol

values could be ascertained in the writer's experiments only by means of small blood samples, the possibility remained that cholesterol stored in various organs, the adrenals and the liver, for instance, had been mobilized in some way by the diet, and that the increase was due to a mobilization rather than to an actual synthesis. Although this deduction seemed plausible, it could not be verified, of course, and the rise of the blood cholesterol on a cholesterol-poor food was by no means explained. Mueller's<sup>34</sup> recent investigations may furnish a satisfactory explanation, however, inasmuch as he was able to show that the pancreas plays a hitherto unsuspected part in cholesterol metabolism. Although it had been known for some time that high cholesterol values are by no means rare, if not constant, in diabetes, the observation had not been accounted for so far as the writer is aware. Mueller<sup>34</sup> analyzed the gastroduodenal content of dogs after cholesterol feeding and studied cholesterol absorption in the digestive tract after elimination of the bile and pancreatic secretion (biliary fistula, ligation or resection of the pancreatic duct). He also studied the effect of the digestive enzymes on cholesterol *in vitro* and found that the pancreatic secretion was needed for the formation of cholesterol esters; that no cholesterol could be absorbed by the intestine without esterification; that no cholesterol absorption took place after ligation of the pancreatic duct; and that biliary fistulas lessened, but did not prevent, the absorption of cholesterol (the latter observation is in contradiction to Rothschild's findings),<sup>41</sup> but that the formation of cholesterol esters was markedly accelerated by the combined action of the bile and the pancreatic juice.

The bearing of Mueller's investigations on our experiment appears to be as follows: It seems possible that as the amount of carbohydrates provided in the oatmeal diet was relatively greater than the amount usually consumed in the mixed diet (though it did not greatly exceed the average carbohydrate requirements suggested by Friedenwald and Ruhrah), the increased demands on carbohydrate metabolism, and especially the sudden change of diet, may have somewhat overtaxed the pancreas. If this deduction be correct, the greater part of the pancreatic secretion may have been used to metabolize the sudden increase of carbohydrates and but little of its activity could have been devoted to the esterification of the body cholesterol. Since free (non-esterized) cholesterol cannot be absorbed by the intestinal mucosa, it would have remained in the circulation, causing a rise in the blood cholesterol. It is to be regretted that Mueller's<sup>34</sup> publication was not available at the



the morphologic differentiation of the nucleus itself. He considers in perfect specimens the varied shapes of the nuclei are neither facts nor instantaneous pictures of some phase of the motility of protoplasm ("... dass die gelappten Kerne der feinkörnigen Kocyten weder Kunstprodukte noch Augenblicksbilder einer durch Protoplasmabewegung ständig ummodellierbaren Krenmasse ohne zisem Formkarakter darstellen") (p. 239). Only perfect cells that show no trace of crushing or friction have been included in the writer's collection as may be seen from the photomicrographs, Figs. 189, 190, 192, 194, and 195. Weidenreich looks upon the more compact and solid irregular disks, Fig. 190, No. 1, for instance (the solid J and L shapes, Fig. 189, Nos. 7, 8, and 9, may perhaps also be included under this heading), as "juvenile forms" (Jugendformen) that pass through various stages of morphologic differentiation as they present the well-known picture of the fragmented nucleus the component parts of which are united by slender threads. The relative position of the fragments may be influenced to a certain extent by the motility of the protoplasm, according to Weidenreich but this motility plays only a secondary part in the morphology of the nucleus. That any circular arrangement of the nuclear fragments is due to the presence of a "central body" (Centralkörper) he considers "out of the question." True rings and figure-of-eight shapes are found in the blood of rats<sup>58</sup> (p. 226). In human blood the overlapping of the ends of the nuclear thread may produce similar shapes, but these should be looked upon as "pseudo-rings." This overlapping can be clearly seen in several of the writer's photomicrographs (Fig. 189, Nos. 4, 8, 9; Fig. 191, No. 6; Fig. 192, Nos. 1, 5, 6; Fig. 195, Nos. 1, 2) though in many instances the process of overlapping can hardly be traced (Fig. 189, Nos. 1, 5; Fig. 191, Nos. 1, 2, 3, 4; Fig. 192, No. 1; Fig. 194, No. 2). Two neutrophils showing a strong resemblance to a figure-eight may be found in Fig. 192, No. 4, and Fig. 195, No. 3. Whatever the cause of the phenomenon may be there seems to be a curious tendency to pseudo-ring formation both in the blood of the carcinoma patient and in that of the writer when the blood cholesterol reaches its maximum. The gradual closing of the ring in the blood of a carcinoma patient may be traced in Fig. 1, No. 3. In the blood of the writer, ring-like forms were found even among the large lymphocytes (Fig. 192, No. 4; Fig. 194, No. 5; Fig. 195, No. 5). The morphologic evolution of the nucleus, described by Weidenreich, is illustrated by a reproduction of one of his illustrations (Fig. 196). The fact that the only cell in the diagrams which bears a close resemblance to the writer's

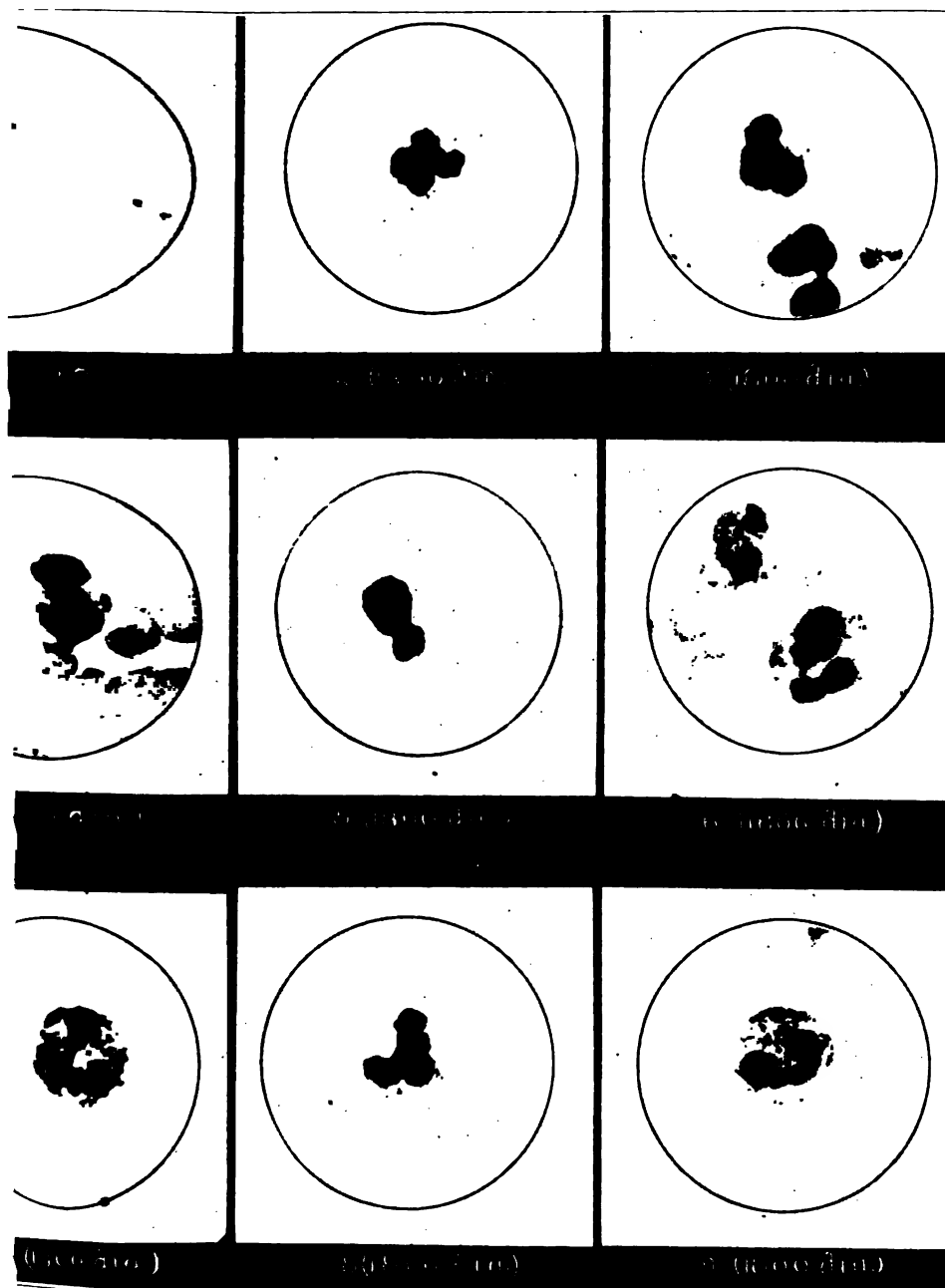


Fig. 190.—Atypical neutrophils in carcinoma of the sigmoid: Bizarre forms.

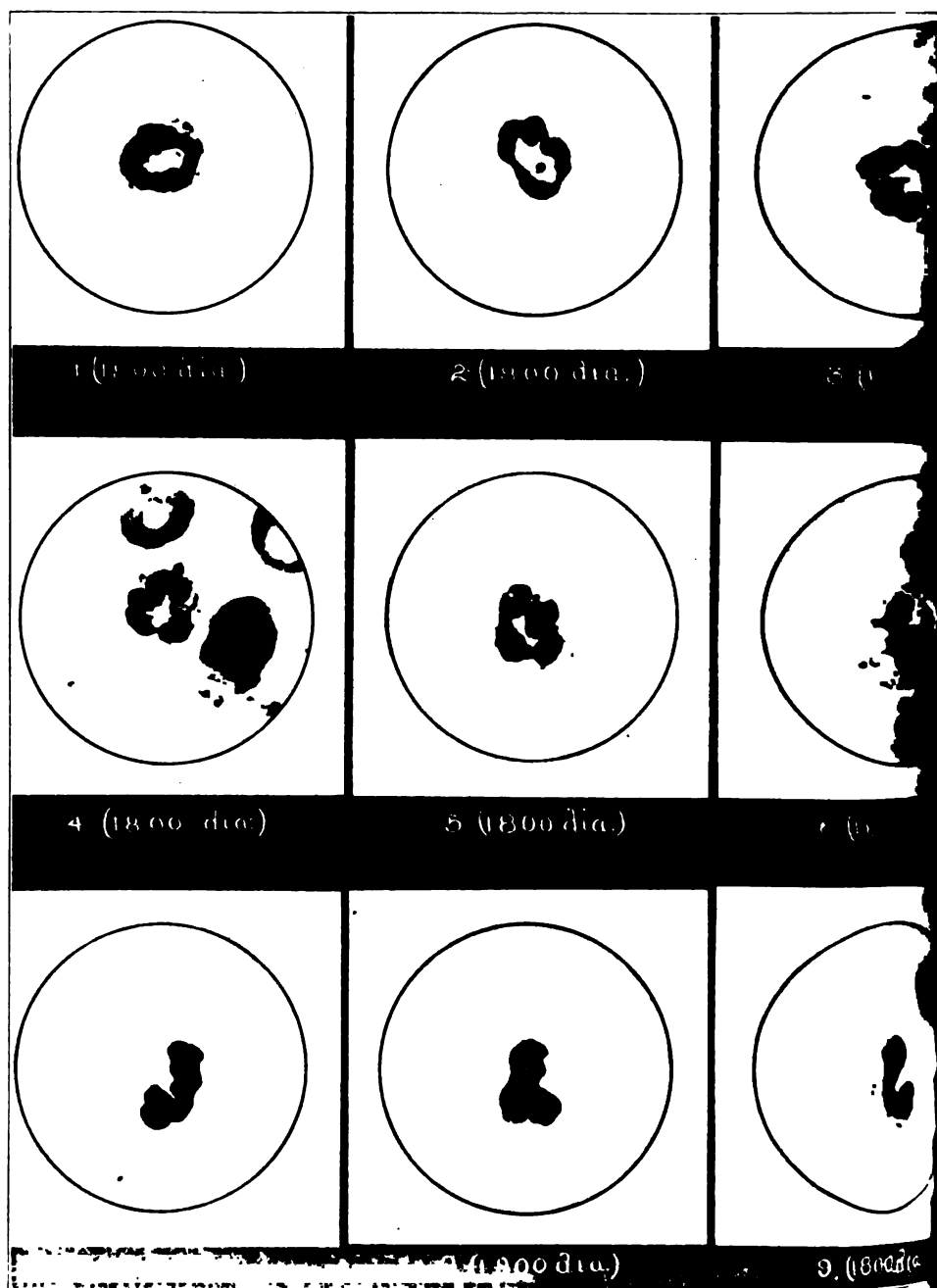


Fig. 191.—Atypical neutrophils in the blood of the writer during exclusive meat diet. (June 27, 1916.) Ringier (1916)  
Bizarre forms, 9 per cent.

micrographs, was found by Weidenreich in leukemic blood (Fig. 196, 6. 1) may be more than a mere coincidence, since the relation of *pernicious anemia*, *pernicious anemia*, and carcinoma has been discussed by hematologists as well as pathologists (Pappenheim, Heinrichsdorff, Slye,<sup>50</sup> and Holmes, and Wells<sup>49</sup>). "The leukemic process is to be regarded as a

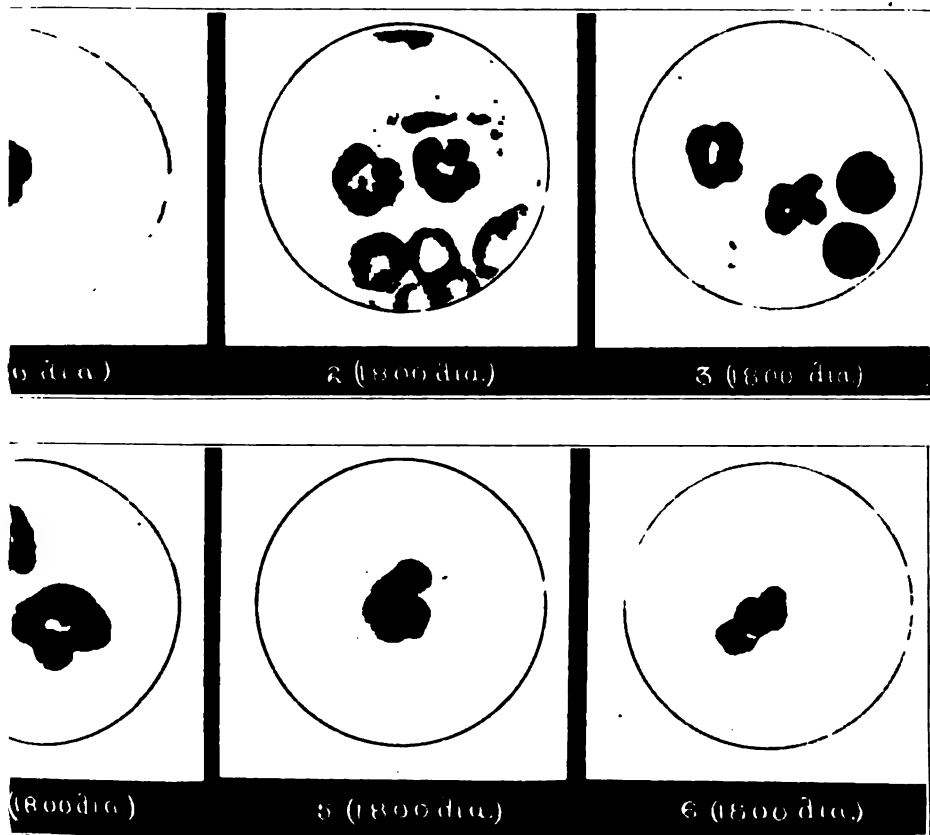


Fig. 192.—Atypical neutrophils in the writer's blood during exclusive meat diet. (June 28, 1916.) Ringforms, 5.0 per cent; Bizarre forms, 5.0 per cent. No. 4, large lymphocyte, lower field.

generalized proliferation (Der leukämische Prozess ist als eine generalisierte Wucherung aufzufassend," Grawitz, p. 244) (Figs. 189, 190, 191, 192, 194, 195 and 196).

Definite conclusions concerning the diagnostic value of these atypical neutrophils are undoubtedly premature, but the fact that their numerical increase is directly proportional to the cholesterol value; that is, the

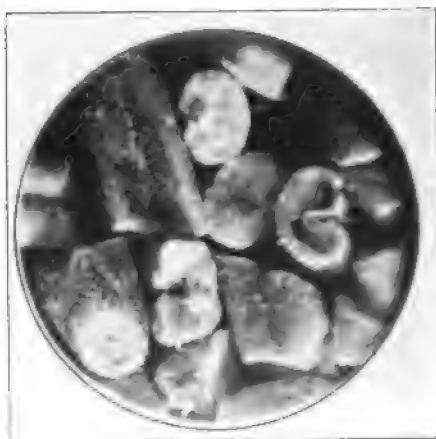
chemical composition of the blood, both in the diet experiments reported and in an advanced case of carcinoma, and inversely proportional to the lymphoid count, may be significant; it recalls W



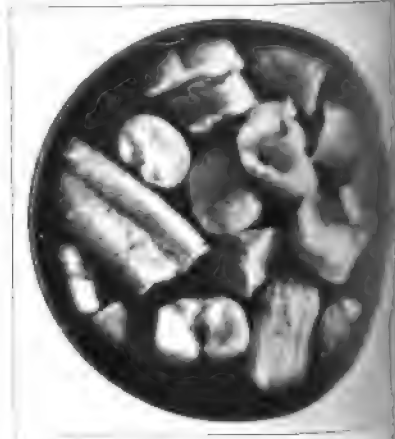
A



B



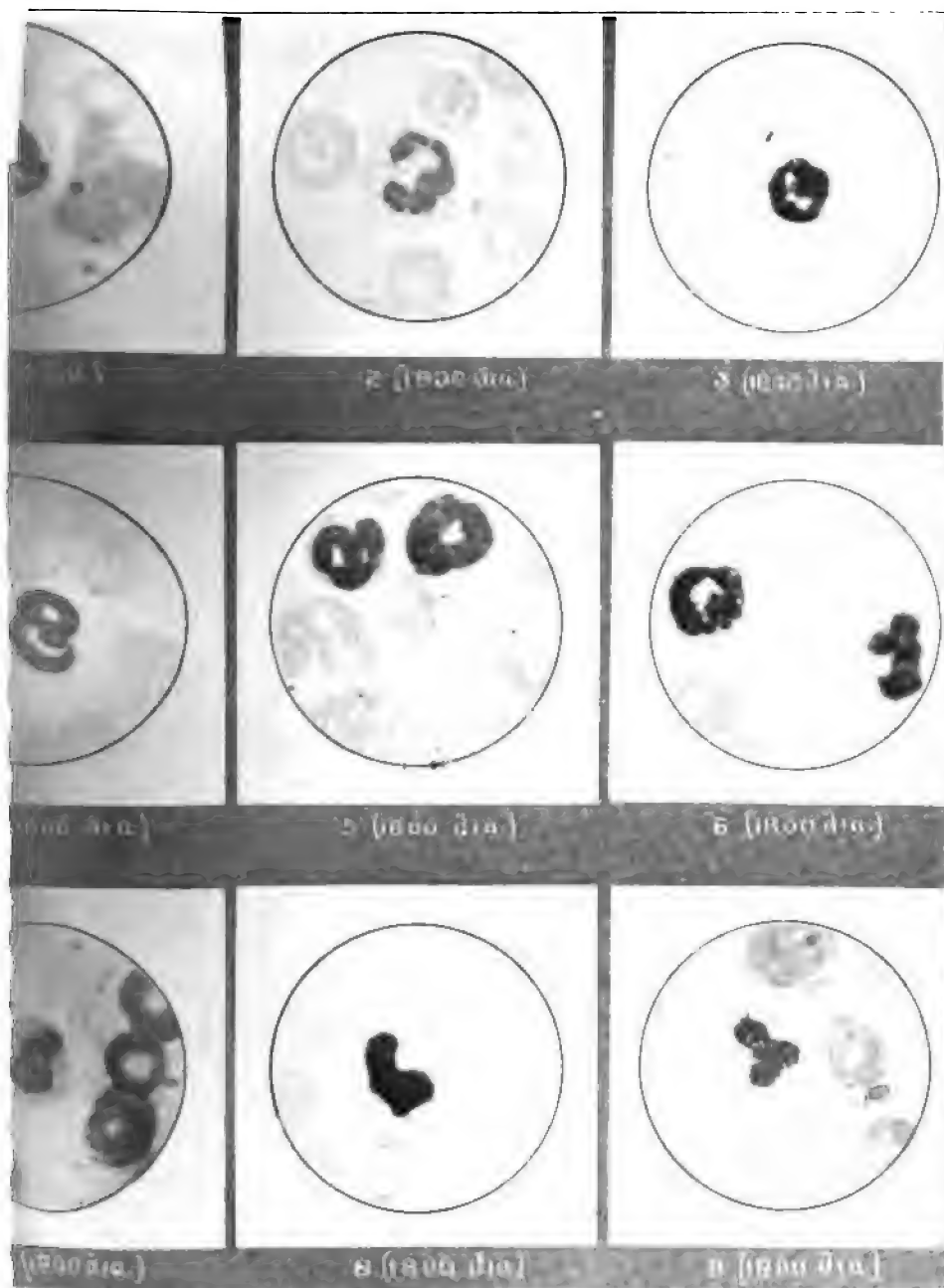
C



D

Fig. 193.—Scotch oatmeal: Broken oats. Observe that the husks about have been removed and the dark hairy capsule is still visible on many of the grains. (Approximately  $\times 10$ .)

reich's suggestion that the study of the atypical leukocytes might be without practical value and "might open up new perspectives" (es wäre nicht unmöglich dass sich dadurch neue Gesichtspunkte gewinnen liessen").



-Atypical neutrophils in the writer's blood during oatmeal diet. (October 31, 1916.) Ringforms 6 per cent; Bizarre forms, 5 per cent. No. 5, large lymphocyte to right.

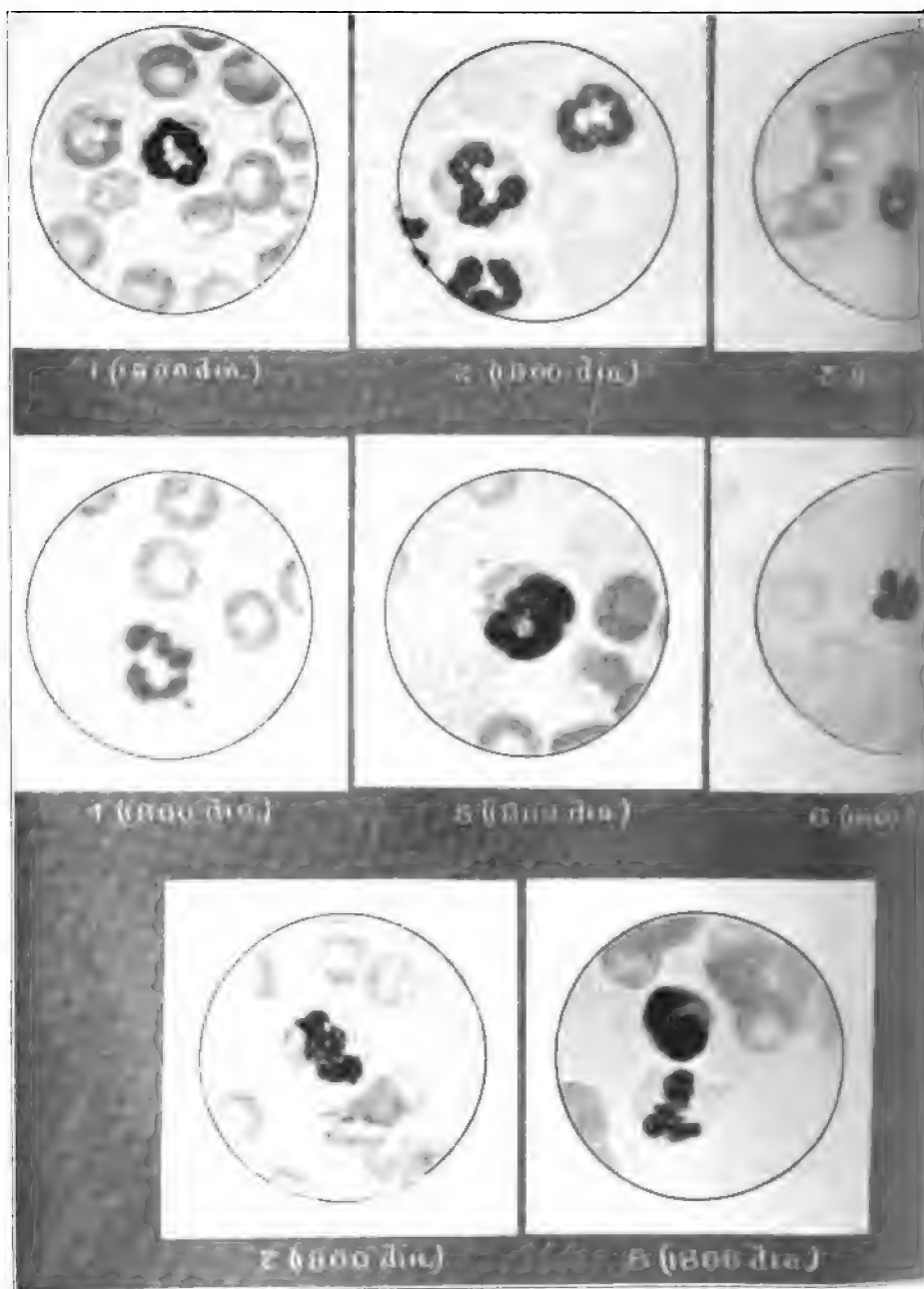


Fig. 195.—Atypical neutrophils in the writer's blood during oatmeal diet. (November 1, 1916.) Ringforms, 6 per cent. No. 5, large lymphocyte.



Fig. 16.—Evolution of the nucleus in the neutrophil polymorphonuclear leukocytes. (After Weidenreich.)  
 No. 15, a to am: Normal human blood. No. 16, a to z: Leukemic human blood. No. 17, a to e: Eosinophile  
 leukocytes in leukemic blood. Observe that the only nucleus of the ring type resembling the writer's photo-  
 micrographs is in the leukemic blood: No. 16, l.



That the chemical composition of the blood can be changed by dietetic measures within a few days has been shown repeatedly in the investigations. The blood cholesterol was reduced by one-third in 4 days by means of Gruner's diet and increased as much in three to 4 days by the meat and oatmeal experiments. Now if the cytology of the blood and even the morphology of the neutrophil leukocytes can be influenced by the chemical composition of the blood to the extent shown in the experiments here reported, it is hardly to be expected that all cells should be insensitive to this influence. We know that the life of every cell in the body depends on its blood supply. We have seen that the chemical composition of the blood depends to a certain extent, at least, on the chemical composition of the diet. If we consider that the dietary conditions may continue unaltered for months and years and that the chemical composition of the blood will affect body cells during the entire period, the influence of the diet on cell growth or cell proliferation cannot be discarded as merely hypothetical.

There is every reason to assume that cholesterol plays a part in the formation of new cells. If we admit that cancer, that is, undue proliferation, almost invariably occurs on the site of old lesions where the normal process of reparative proliferation is already active and further stimulation will be most readily responded to, the significance of the cholesterol content of the blood cannot be ignored.

The inheritability of the tendency to tumor formation has been proved repeatedly by Slye<sup>49,50,51,52,53</sup> in her observations on mice, and the inheritability of specific organs has been shown conclusively by her brilliant report on tumors of the liver<sup>52</sup> in the same animals. In this report 62 primary liver tumors could be traced in the direct descendants of one female mouse with a malignant adenoma of the liver and a sarcoma of the mammary gland.\*

The number of liver tumors and their spontaneous transmission in Slye's mice are equally remarkable, as only one tumor of the liver in mice has been reported elsewhere. From the inheritability of specially disposed organs the hereditary transmission of inadequate organs may be logically deduced, and if the organs thus transmitted should be among those that take a prominent part in metabolic function (the liver, for instance), faulty metabolism can reasonably be expected in the genera-

\* Slye's mice are used for breeding purposes only and the tumors found among them are spontaneous growths in every instance. The incidence of spontaneous tumors in rats has been studied lately by Bullock and Rohdenburg.

tions that inherit such organs. The tendency shown by certain types of cancer to appear in various members of human families is not unknown in medical circles,<sup>22,38,60</sup> and the assumption that the influence of metabolism on this tendency may be important is supported by Burrows' conclusions from his experiments on the growth of tissue *in vitro*: "If these experiments are substantiated . . . the problem of cell growth is brought into the domain of chemistry. Thus problems, such as confront us in cancer, are greatly narrowed." It is the writer's conviction that faulty metabolism; that is, the inability of the organism to metabolize certain kinds of food (meat may be among these), may play a far greater part in the incidence of cancer than has hitherto been generally accepted.

### CONCLUSIONS

A consideration of the work of other observers and of the writer's experiments herein detailed seems to warrant the following conclusions:

1. The influence of the chemical composition of the food on the chemical composition of the blood in increasing or diminishing the amount of cholesterol therein is clearly demonstrated.

2. A diet which increases the blood cholesterol coincidentally weakens the lymphoid defense.

3. A diet which reduces the blood cholesterol coincidentally increases the lymphoid defense.

4. In persons predisposed to carcinoma an increase of the cholesterol and a weakening of the lymphoid defense, such as may occur with the prolonged use of a diet adapted thereto, may perhaps result in the development of carcinoma.

5. Dietetic measures calculated to reduce the blood cholesterol and coincidentally increase the lymphoid defense may yet prove to be of value in the treatment of carcinoma.

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## V. THE BLOOD CHOLESTEROL IN MALIGNANT DISEASE AND THE EFFECT OF RADIUM ON THE BLOOD CHOLESTEROL

It is universally conceded that the life of every cell in the body depends on its blood supply. It has repeatedly been demonstrated that malignant cells are aberrant though lineal descendants of normal cells,<sup>19, 35, 47, 56, 57</sup> and it would seem a foregone conclusion that cell-like individuals, must be influenced by the conditions under which they exist. Yet, strange as it may seem, little attention has been paid to the fact that the chemical composition of the blood must affect the cell as vitally as does their blood supply.

Compared with the immense amount of work that has been done on cancer from the cellular point of view, the attention given to the chemical composition of the blood in cancer has been woefully small. Blood,<sup>13, 20, 46, 47, 49, 53</sup> Serum,<sup>12, 18, 27, 52, 54, 66</sup> Nevertheless the observations of Benedict and Lewis<sup>4</sup> on the increase of the blood sugar content in carcinoma, Menten's<sup>43</sup> report on the increased alkalinity of the blood and Bloor's<sup>5, 8</sup> work on the blood lipoids must be looked upon as landmarks in the study of malignant disease. I am convinced that physiologic chemistry will not only explain the causation, but eventually find the cure for cancer.

In no field of cancer research has the chemical composition of the blood received less attention than in radium therapy. The effect of radium seems to have been studied entirely from the cellular point of view.<sup>44, 45, 60, 14</sup> In Colwell and Russ' recent monograph, for instance, data are given on the cytology of the blood following radium treatment, but the chemical composition of the blood is not even mentioned, although a whole chapter is devoted to the chemical action of radium on various substances.

Robertson and Burnett's<sup>48</sup> publication on the rapid growth of tumor transplants in rats following intravenous injections of cholesterol, first called my attention to the cholesterol content of the blood and its possible relation to malignant disease.<sup>34</sup> The idea that cholesterol might in some way promote cell-proliferation seemed to be supported by the increase of the blood cholesterol in pregnancy and its return to normal after delivery,<sup>1, 2, 3, 10, 51, 52</sup> as well as by Browder's report on the increased rate of division in paramecium when cholesterol is added to the culture-medium.

between November, 1915, and December, 1917, I tested 1069 samples of cholesterol. This number included 1052 determinations of blood cholesterol (human, goat, gopher, and dog's blood), 14 determinations of rodstuffs, and 3 on human pus. Of 743 blood samples parallel determinations in triplicate were made with Bloor's original method (Bloor I with sodium ethylate) and with its modification (Bloor II without

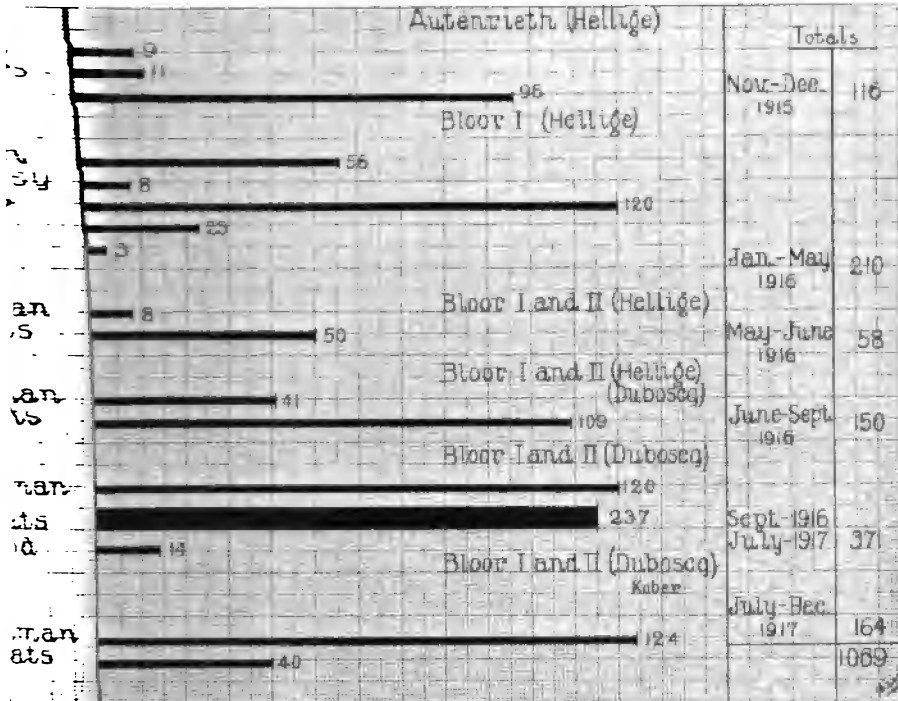


Fig. 197.—Cholesterol determinations made by the writer from November, 1915, to December, 1917. Methods used: Autenrieth-Funk, Bloor I, II. Bloor I, II, indicates parallel determinations with both methods. Colorimeters: Hellige, Hellige-Duboscq, Duboscq-Kober. Hyphenated designation of two colorimeters indicates parallel determinations with both instruments. Samples used in determinations are given in margin: human blood, goat's blood, human pus, etc. Fourth entry from the bottom has been drawn in double width on account of the number of determinations made; goat's blood, 237.

sodium ethylate),<sup>5,6</sup> making a total of 4658 determinations with Bloor's methods. The advantage of these parallel determinations, by which the amount of cholesterol split products present in the blood is revealed, was shown by 2196 tests made on pathologic human blood, including 70 miscellaneous conditions, 41 cases of pernicious anemia, 37 of exophthalmic goiter, 3 of myxedema tested 18 times at various intervals during the administration of the thyroid hormone (Kendall's thyroxin),

79 determinations on my own blood as normal controls and on experimental diets,<sup>31</sup> 9 cases of sarcoma (16 determinations) and determinations on the blood cholesterol in carcinoma before and after radium treatment, including 20 weekly determinations on one patient (Figs. 197 and 198). The technic used in my determinations has been published previously.<sup>33, 34</sup>

Two points should be mentioned in connection with the technique. First, the two types found in human blood (Figs. 199 and 200), to which

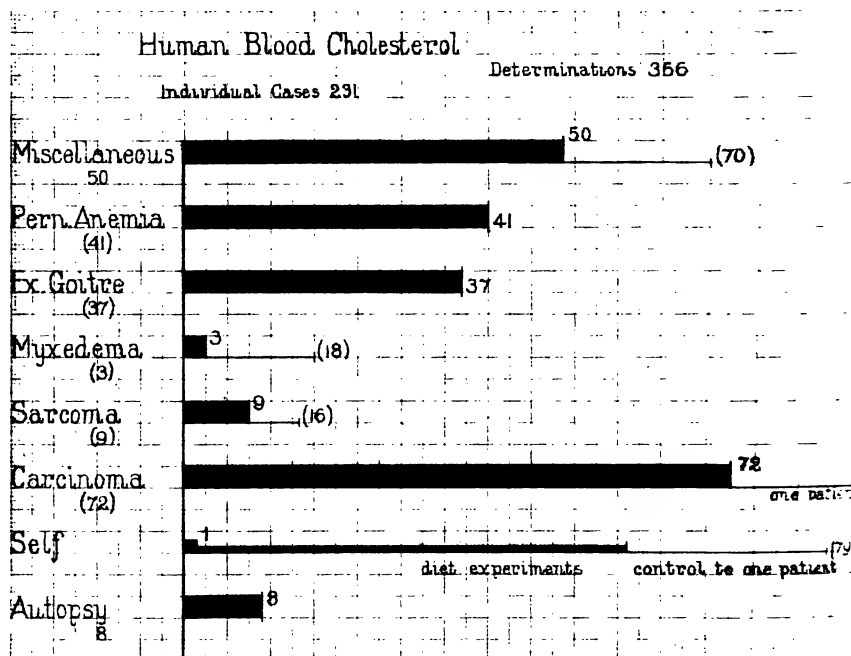


Fig. 198.—Human blood, cholesterol determinations under various conditions. Wide bar denotes number of determinations made on individual cases. Narrow bar and number in brackets denotes additional determinations on the same person. Necropsy: blood taken at necropsy at different number of hours after death to study effect of postmortem changes. Cholesterol values were unchanged.

called attention in my second study on cholesterol,<sup>34</sup> and which have since also been observed by Bloor,<sup>8</sup> and second, the value of parallel determinations with the Bloor I and Bloor II methods.<sup>34</sup>

*Advantage of parallel determinations with Bloor I and II methods.*—Lifschütz<sup>28-33</sup> has shown that certain bile salts and bile acids are cholesterol split-products. These bile derivatives are eliminated in the Bloor I method by the use of sodium ethylate. In the Bloor II method no sodium ethylate is used and the tests contain both cholesterol and bile deriva-

The difference between the Bloor I and Bloor II tests, therefore, represents the amount of bile derivatives<sup>24</sup> present in the blood sample. Absence of difference between the two tests, or equal values by the Bloor I and Bloor II methods, indicates some inability on the part of the organism to oxidize its blood cholesterol to bile derivatives; in other words, some disturbance of cholesterol metabolism. In normal blood there is always a difference between the Bloor I and Bloor II values, but in carcinoma this difference is absent in a high percentage of cases

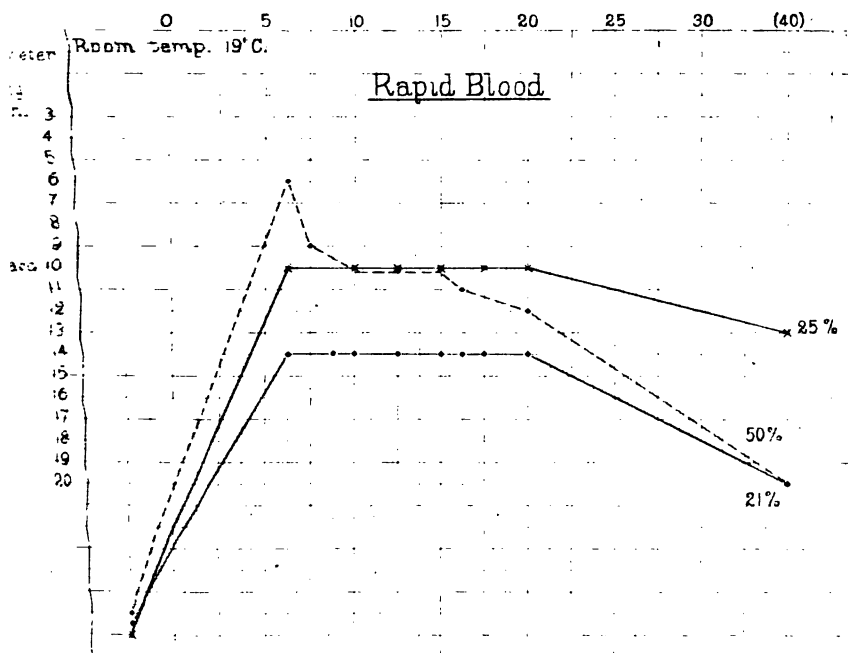


Fig. 199.—Types of reaction in cholesterol determinations on human blood. Rapid blood ripens more quickly than cholesterol standard test. X-X-X—: Cholesterol standard test. ———, Bloor I test. - - -, Bloor II test. Numbers in margin denote mm. on Duboscq colorimeter. Percentage of loss of original maximum color value in forty minutes indicated at the end of each curve.

(53-56 per cent in our determinations) and we find equal values with both tests. In a series of 252 determinations in non-malignant cases I have not observed equal values; however, this does not signify that equal values are to be looked upon as unmistakable diagnostic evidence. The test for cholesterol in the blood is a clinical test capable of giving valuable information, but it is not, unfortunately, as so often has been thought, a diagnostic test. It is not expected that the test for albumin in the urine or the hemoglobin test should furnish a conclusive differ-



ential diagnosis, nor should any such evidence be expected from the blood cholesterol test. The unwarranted assumption that blood cholesterol determinations should settle diagnoses has done much to discredit the value of such determinations in the eyes of clinicians, and valuable information concerning metabolic problems must have been lost in consequence.

*Cholesterol values found in human blood.*—In my previous publications<sup>34</sup> the values reported have been based on the amount of cholesterol

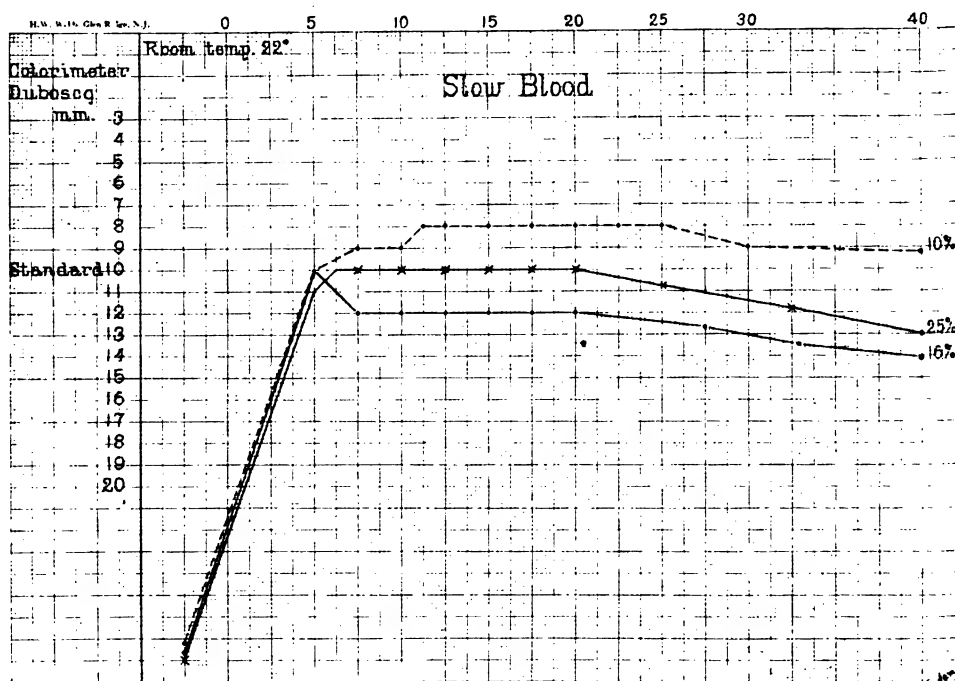


Fig. 200.—Slow blood ripens more slowly than cholesterol standard test. (Explanatory notes the same as for Fig. 199.)

in milligrams found in each determination or test, that is, in 6 c.c. of the chloroform extract representing 0.3 c.c. of whole blood. The foregoing values might, therefore, be designated as "test values." Since a uniform terminology based on mg. per 100 c.c. has been adopted for determinations of other blood constituents, blood urea and blood sugar, as well as for blood cholesterol, and as it is highly desirable that a standardized procedure for blood cholesterol determinations should be adopted by all workers in this field of blood chemistry, the values found

in our determinations will in future be expressed in milligrams per 100 c.c. only. The test values referred to may be converted into milligrams per 100 c.c. of whole blood by simply dividing by 3, the values given in my previous publications. The Bloor I method will remain the basis of comparison, as has been the case in previous publications. The Bloor II values show much greater fluctuations even in the blood of the same individual taken at different times, and the factors that cause these fluctuations are not all fully explained, since the fluctuations themselves depend on the rate of cholesterol metabolism.

**BLOOD CHOLESTEROL VALUES WITH THE BLOOR I METHOD: MILLIGRAM OF CHOLESTEROL PER 100 C.C. OF WHOLE BLOOD**

1. Normal values, 70–100 mg., found in healthy persons on mixed diet, digestion being duly excluded, in exophthalmic goiter and in some cases of sarcoma.
2. Increased values, 100–140 mg., found during the process of digestion and in various more or less pathologic conditions.
3. High values, 140–200 mg., found associated with pathologic conditions only.
4. Unusual values, over 200 mg., found in cases of myxedema and in some cases of carcinoma.

This classification of values is based on over 2000 determinations; it was adopted for practical purposes only, and represents the values I have observed, but should not be looked on as a diagnostic classification, since the cholesterol test does not furnish conclusive diagnostic evidence. That higher values have been reported as normal must be accounted for by the methods and the technic by which those values were obtained, such, for example, as leaving the tests in the dark for fifteen minutes at a relatively high temperature<sup>34</sup> and by the two types of reaction found in human blood. It is obvious that if a sample of "slow" blood is tested against a "fading" standard, the values obtained must be relatively higher.

*Blood cholesterol values in patients suffering from carcinoma.*—High values are generally found in cases of carcinoma; they were found in 43 per cent of all our cancer patients and in 56 per cent of those who were to have radium treatment. I am at a loss to understand how Denis<sup>13</sup> came to the conclusion that I had reported low values in connection with cancer cachexia, as this condition is not even mentioned in the article to which they refer. Several of our patients, moreover, with high values

showed distinct symptoms of cachexia. But as the technic used cholesterol determinations controls the values to a considerable extent a uniform technic alone can assure comparable values.

For the sake of comparison with patients suffering from carcinoma a group of 70 patients suffering with various non-malignant conditions such as tonsillitis, gastric disturbances, biliary disturbances, etc., diseases, malaria, etc., was tabulated similarly to the 72 cancer cases. No equal values were found in this group and high values occurred only 10 per cent, increased and normal values being found in 41 and 49 per cent respectively.

TABLE 1.—CHOLESTEROL VALUES IN CARCINOMA (CASES DIAGNOSED CLINICALLY AND MICROSCOPICALLY AND CLINICALLY ONLY)

CASES—72	CASES TESTED WITH BLOOD I AND II —65	EQUAL VALUES 65 CASES 22 (34 PER CENT)
High values... 31 (43 per cent)	High values... 24 (37 per cent)	24 cases... 13 (54 per cent)
Increased values... 26 (36 per cent)	Increased values... 26 (40 per cent)	26 cases... 4 (15 per cent)
Normal values 15 (20 per cent)	Normal values 15 (23 per cent)	15 cases... 1 (6.6 per cent)

TABLE 2.—CARCINOMA CASES BEFORE RADIUM TREATMENT

CASES—55	CASES TESTED WITH BLOOD I AND II —48	EQUAL VALUES 48 CASES 16 (33 PER CENT)
High values... 31 (56 per cent)	High values... 24 (50 per cent)	24 cases... 13 (54 per cent)
Increased values... 14 (25 per cent)	Increased values... 14 (29 per cent)	14 cases... 4 (28 per cent)
Normal values 10 (18 per cent)	Normal values 10 (20 per cent)	10 cases... 1 (10 per cent)

TABLE 3.—MISCELLANEOUS CASES, PATHOLOGIC BUT NON-MALIGNANT

CASES—70	CASES TESTED WITH BLOOD I AND II —70	EQUAL VALUES 0
High values... 7 (10 per cent)	High values... 7 (10 per cent)	0
Increased values... 29 (41 per cent)	Increased values... 29 (41 per cent)	0
Normal values 34 (49 per cent)	Normal values 34 (49 per cent)	0

*Reduction of the Blood I values and increase of the Blood II values under radium treatment.*—The influence of radium treatment on the blood cholesterol values is clearly shown by a group of 17 patients whose blood was tested before and after radium treatment. In this group there is a

ted change in the relation of high, increased, and normal values. reas high values preponderate in cases of carcinoma before radium timent, the percentage of high values is lowest of all in this group the equal values have completely disappeared (Figs. 201 and 202).

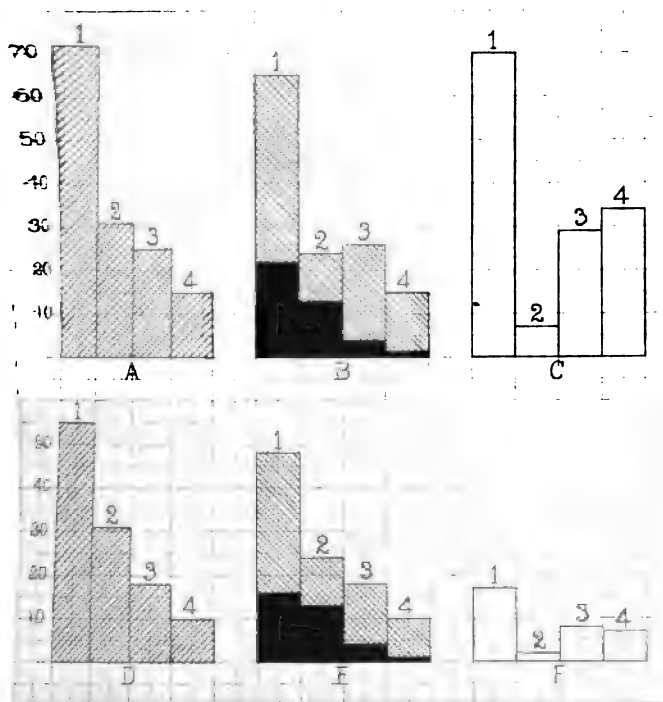


Fig. 201.—Blood cholesterol values given in numbers of cases. 1. Total number of cases. 2. Total number of cases with high values. 3. Total number of cases with increased values. 4. Total number of cases with normal values. ■ = Equal values. A. Relation of high, increased, and normal values in all the determinations on carcinoma (various methods). B. Relation of high, increased, and normal values in determinations on carcinoma with Bloor I and Bloor II methods. Note preponderance of high equal values in B 2. C. Miscellaneous, non-malignant cases, no equal values (Bloor I, II). D. Relation of high, increased, and normal values in all the determinations on carcinoma before radium treatment (various methods). E. Relation of high, increased, and normal values in carcinoma cases tested (Bloor I and II) before radium treatment. Note relative increase of both high and equal values. F. Relation of high, increased, and normal values in carcinoma after radium treatment (tested with Bloor I, II). Observe the disappearance of the equal values and the great relative decrease of high values, which makes this diagram similar to diagram C.

TABLE 4.—CARCINOMA CASES AFTER RADIUM TREATMENT

Cases—17		EQUAL VALUES
High values.....	2 (11 per cent)	0
Increased values.....	8 (47 per cent)	0
Normal values.....	7 (41 per cent)	0

All these cases were tested with the Bloor I and Bloor II methods. That the drop of the Bloor I values is accompanied by an increase of the Bloor II values, resulting in an increased difference between the

values found by Bloor's two methods, is graphically illustrated by Figures 203 and 204. Since, as has been previously pointed out, this difference is due to bile derivatives, which must be looked on as oxidized or changed cholesterol,<sup>34</sup> it is obvious that radium treatment in some way accelerates the rate of cholesterol metabolism. Although the process by which these metabolic changes are brought about is by no means fully explained, the fact remains that the chemical composition of the blood is

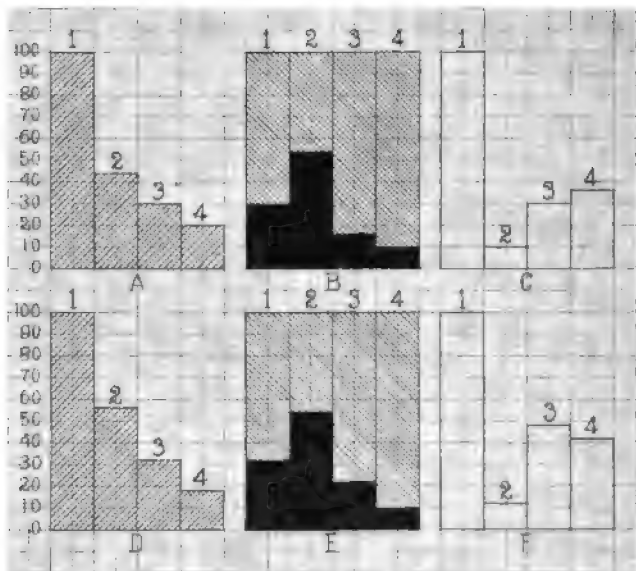


Fig. 204.—Relation of high, increased, and normal blood cholesterol values. (Given in percentage of cases.) 1. Total of determinations in percentage of cases. 2. High values in percentage of cases. 3. Increased values in percentage of cases. 4. Normal values in percentage of cases. ■ = Equal values in percentage of cases. A. Relation of values in all the carcinoma cases (various methods of extraction). B. Percentage of equal values. Observe preponderance of 2 (high values) (Bloor I, II). C. Miscellaneous, non-malignant cases; no equal values (Bloor I, II). D. Relation of values in carcinoma before radium treatment (Bloor I, II). E. Percentage of equal values in carcinoma before radium treatment (Bloor I, II). Observe preponderance of high, equal values. F. Relation of values in carcinoma after radium treatment. Observe disappearance of equal values and the striking reduction of high values which cause this diagram to resemble diagram C.

changed by radium treatment and it seems probable that the beneficial effect of radium in cases of malignancy may be largely due to this fact. In sarcoma the blood cholesterol values appear to be lower on the whole than in carcinoma, but equal values were found in 2 of our 9 cases (22 per cent) and the effect of radium on the blood cholesterol is identical: namely, a reduction of the Bloor I values and an increased difference between the Bloor I and Bloor II tests (Figs. 203 and 204).

That the high blood cholesterol values observed in cases of carcinoma

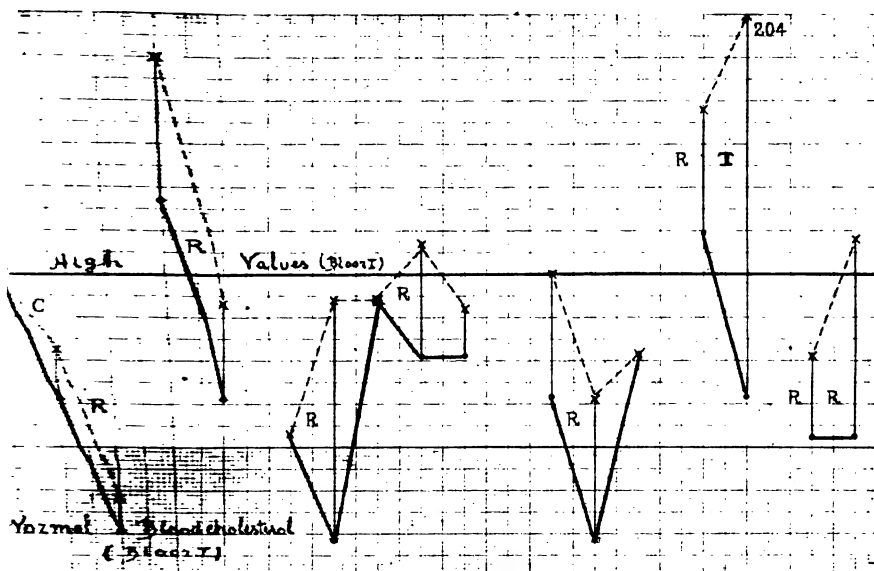


Fig. 203.—Curve showing drop of Bloor I values and increase of Bloor II values in carcinoma after radium treatment. (6 cases.) —, Bloor I test. ---, Bloor II test. R, radium treatment. T, 6 mg. of thyroxin. In Case 1 the difference between Bloor I and II is not greatly increased even after radium treatment. The patient has since died. Case 2, marked difference even before radium treatment. Complete remission. Cases 3, 4, 5, and 6 doing well; in Case 4 the presence of carcinoma suggested by the equal values was confirmed by excision and microscopic findings (lupus erythematosus going over into carcinoma). In Case 6, mg. of thyroxin was given at patient's request. Patient left for South Africa.

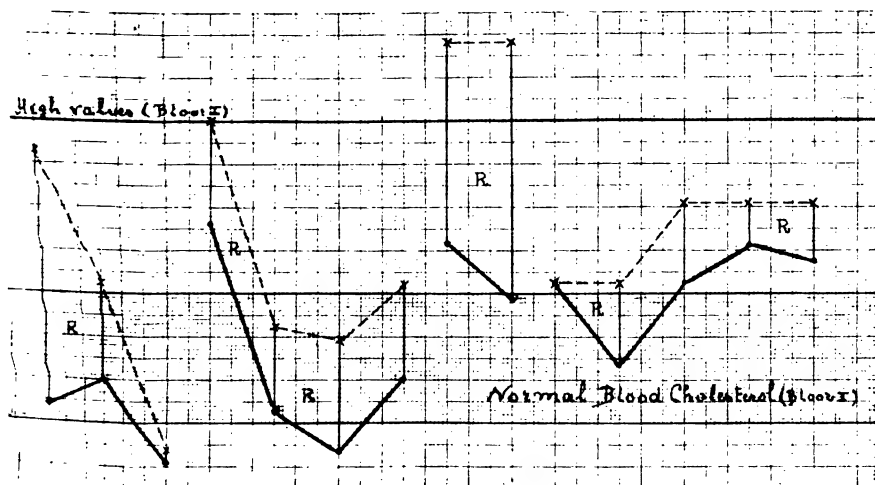


Fig. 204.—Curve showing effect of radium treatment in sarcoma. (4 cases.) Note that the values are lower on the whole than in carcinoma and note the reduction of the Bloor I with parallel increase of the Bloor II values, and the disappearance of the equal values after radium treatment in Case 4. Radium treatment.

responsible for the high blood cholesterol values that are commonly found in carcinoma.

Aside from the effect of radium on metabolic processes and thereby indirectly on the chemical composition of the blood, the following considerations may help to account for the reduction of the blood cholesterol (Bloor I) following radium treatment. Schulze and Winterstein<sup>50</sup> have shown that cholesterol is oxidized and disintegrated by the action

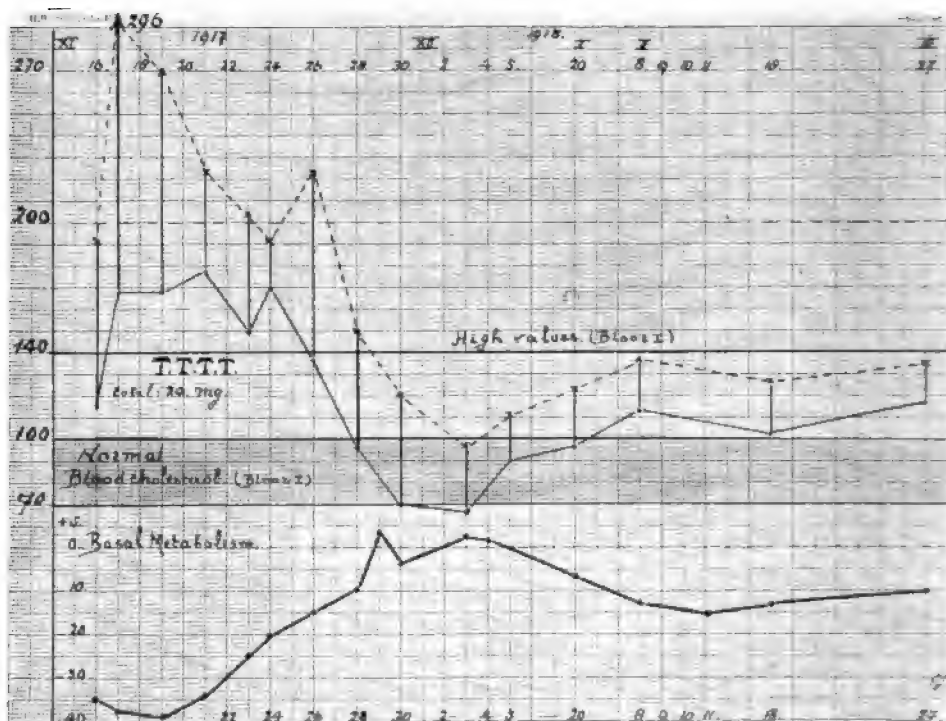


Fig. 207.—(The same as Fig. 205 ) T, thyroxin, 5 mg. at each dose. Patient went home perfectly well.

of light. It is known that radium is photoactive. It is possible, therefore, that the photochemical activity of radium may cause the changes observed in the cholesterol content of the blood after radium treatment. The increase of the cholesterol split products in the blood, namely, the increased difference between Bloor I and II, supports this interpretation.

If we compare the disintegration of cholesterol in the body to the combustion of fuel by fire, changed or oxidized cholesterol may be

compared to fuel that has been consumed and thus rendered harmless, whereas pure, unchanged cholesterol may be compared to fuel that has not yet been consumed. An accumulation of unconsumed fuel contains in itself the latent possibility of starting a conflagration. It is possible that, although we know pure cholesterol promotes cell division, changed cholesterol may fail to do so. A high percentage of unchanged cholesterol, such as is found in carcinoma, would therefore represent an opportunity for undue cell proliferation that is an element of danger. This danger appears to be reduced or eliminated by the action of radium since it is found that the amount of changed (possibly harmless) cholesterol increases in the blood as the condition of the patient is improved by radium therapy.\*

The reduction of the blood cholesterol values by the administration of the thyroxin in myxedema, however, cannot be looked upon as the result of photochemical activity. The thyroid hormone is not photoactive. Nevertheless the blood cholesterol values are lowered by the use of thyroxin as well as by radium treatment. We know that the thyroid hormone is capable of increasing the rate of basal metabolism, and Figures 206 and 207 show that increased metabolism is accompanied by a reduction of the cholesterol content (Bloor I) of the blood similar to that produced by radium treatment. This fact, whatever the chemical or physiologic process to which it is due may prove to be, shows that the effect of thyroxin on the chemical composition of the blood is similar to that of radium. It also suggests that, since the beneficial effects of radium therapy are well known, the condition of patients suffering from carcinoma may be improved by the administration of thyroid hormone. The relation of thyroid activity to the development of carcinoma has often been discussed,<sup>59</sup> but so far as I am aware the influence of thyroid activity on the cholesterol content of the blood has not been taken into consideration in relation to cancer. The following facts are noteworthy, however: Fourteen cases of spontaneous recovery from cancer in man have been reported by Gaylord and Clowes<sup>16</sup> and two similar

\* Shortly after this paper was read, T. Brailsford Robertson published his observations on cholesterol derivatives, which appear to confirm the above interpretation. (*Journal of Cancer Research*, 1918, iii, 74-90.) Robertson found that by substituting the OH group of the hydroxybenzol radical in the cholesterol molecule he obtained substances which did not accelerate the growth of tumor grafts, whereas he had demonstrated previously that the unchanged cholesterol molecule was capable of so doing. His conclusion should be read in the original article, as it is impossible to do justice to the importance of his observations in this brief reference to them.



cases have occurred to my knowledge\* (a microscopic diagnosis made in every instance). The patients in question had been pronounced "hopeless cases" and received no further treatment. Nevertheless the condition improved to such an extent that they could be looked upon as "cured" from a clinical as well as from a practical point of view. The deduction seems admissible that these patients were able in some way to recover their metabolic balance, notwithstanding the fact that they appeared to be no hope for them. We know that in the majority of instances carcinoma occurs when the first vigor of youth is past, and when metabolism in general tends to become sluggish; when the body, in fact, might be compared to a badly burning fire. The decreased metabolic activity, caused or accompanied by a decreased functional activity of certain glands, is likely to result in the retarded combustion of the substances that are taken in with the food. It has been shown that the cholesterol content of the blood can be increased and reduced at will by the composition of the diet.<sup>34</sup> The administration of a hormone which is known to increase the metabolic rate might therefore provide the stimulus which the body itself is incapable of supplying, and by increasing metabolism assist the body in recovering its balance of health. If in sixteen cases the human body has proved itself equal to this task without assistance it might be able to do so in others with the right kind of assistance. The deduction seems logical; time alone can show if it is correct.

#### SUMMARY

Cholesterol promotes cell multiplication; high blood cholesterol values must, therefore, further malignant growth. High blood cholesterol values are commonly found in carcinoma. Radium treatment and the administration of the thyroid hormone both reduce the cholesterol content (Bloor I) of the blood and increase the amount of changed cholesterol in the blood (namely, the difference between the Bloor I and II values). The high cholesterol values in myxedema are brought

\* One was an inoperable case of pelvic carcinoma, in which the cancer was found to have disappeared several years later at an emergency laparotomy by Kümmell (personal communication by H. R. Gaylord); the other a case of sarcoma of the stomach, the patient operated on at the Brooklyn Hospital, New York, in 1908. The patient was not expected to live beyond two years but is well and active today. His history will be reported when the details of the case have been obtained. In both cases a microscopic diagnosis was made. H. R. Gaylord expressed the opinion that spontaneous recovery from carcinoma would not be found as uncommon as is generally believed, if surgeons were able to keep track of all their patients.

down to normal by the administration of the thyroid hormone at a rate parallel to the rise in basal metabolism induced by the latter.

### CONCLUSIONS

1. The test for cholesterol in the blood is not a diagnostic but merely a clinical test giving valuable information concerning cholesterol metabolism.

2. The high cholesterol values commonly found in carcinoma are not due to cell destruction, since they are reduced by radium treatment, although radium causes cell destruction; they must therefore be due to a disturbance of cholesterol metabolism.

3. The disturbance of cholesterol metabolism may be but an evidence of a subnormal rate of basal metabolism, since the high cholesterol values in myxedema are reduced by the administration of the thyroid hormone (thyroxin) by which the rate of basal metabolism is greatly increased.

4. The disturbance of cholesterol metabolism in carcinoma is revealed by the absence of changed cholesterol or cholesterol split products in the blood of a high percentage of cancer patients, as is shown by the lack of a difference between the cholesterol values obtained by the Bloor I and Bloor II methods, since the writer constantly found such a difference in normal blood and in pathologic but non-malignant conditions.

5. Radium treatment by reducing the unchanged cholesterol (Bloor I values) and increasing the changed cholesterol (difference between Bloor I and II values) affects the chemical composition of the blood—a fact that has not hitherto been taken into account, but which may play an important part in the beneficial effect of radium therapy.

6. Thyroxin affects the blood cholesterol values in a manner similar to that of radium and may therefore also be expected to improve the condition of patients suffering from carcinoma. Careful investigation will, however, be needed before definite conclusions can be drawn concerning the effect of thyroxin on carcinoma, as various metabolic factors may have to be taken into account.

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percentage strength, the chief difference lying in the method of making the various solutions and of reading and reporting end-points, or degrees of hemolysis.

Karsner and Pearce employed Theobald Smith's method, as modified by Gay. "Chemically pure sodium chlorid was dried for two hours at 170° C. and immediately weighed in amounts necessary to make 500 c.c. of volumes of salt solution, ranging from 0.1 to 0.5 per cent in steps of 0.1 per cent. In order to be sure of approximately the same volume of corpuscles in the anemic as in the normal bloods, the gently defibrinated blood was centrifuged and the serum drawn off. One-tenth centimeter of the corpuscular mass was measured in a graduated pipet and placed in 3 c.c. of each of the various salt solutions. Standard colorimetric scales for comparison were made by laking red cells with distilled water; thus the laking of 0.4 c.c. of the corpuscular mass in 12 c.c. of distilled water represented a standard of 100 per cent hemolysis. Dilutions of this solution were made so as to have tubes showing the color values of 80, 60, 40, and 20 per cent hemolysis." Preliminary readings were made, and the mixtures placed in the incubator for eighteen hours when the results were finally read.

Butler describes his technic in detail. The essential difference in his method from others is in the manner of making his mixtures of blood and saline. He uses a Wright capillary pipet of fine bore with an arbitrary unit of measurement marked on the capillary portion of the tube. This small pipet is used for measuring nine units of saline solution of definite percentage strength into a miniature test-tube made from 1/4-inch glass tubing cut off in 1 1/2-inch lengths and sealed at one end. This procedure is repeated, using each one of the different stock saline solutions made fresh each day from a stock 1 per cent sodium chlorid solution. Butler uses a buret for making dilutions of 1 per cent sodium chlorid with distilled water in intervals of strength of 0.025 per cent. Generally the range employed is from 0.45 per cent to 0.30 per cent. In a few instances the strongest solution is 0.7 per cent. A single unit of blood drawn in the Wright pipet from a puncture of the thumb is added to each of the small test-tubes containing nine units of saline, so that his final mixture is always 1 to 10.

Hill has recently reported a method in which he used a definite amount of washed corpuscles (0.05 c.c.) in hypotonic salt solutions of different percentages.

The method of Ribierre has seemed to us to be the most satisfactory.

simple method of accurately determining the fragility of erythrocytes. This author uses a stock solution of 0.5 per cent sodium chlorid. In a series of small test-tubes he places different amounts of this stock solution: in the first tube, 50 drops; in the second, 48; in the third, 46, etc. To each tube are then added the number of drops of distilled water necessary to make the total volume of solution in each tube 50 drops. A definite amount of blood (20 cm.) measured with a graduated capillary pipet is added to each tube of solution. The various degrees of hemolysis from "slight" to "complete" are noted. Normally, hemolysis begins in the tube containing 44 drops of 0.5 per cent salt solution. The percentage of salt in this tube is  $\frac{44}{50}$  of 0.5 per cent, or 0.44 per cent. Our own modification of this method in detail is as follows:

The stock solution is made by dissolving 0.5 gm. sodium chlorid (chemically pure and anhydrous) in 100 c.c. distilled water. Great care should be exercised in making this solution. A good balance must be used for weighing the salt, and a volumetric flask employed for measuring the water.

A twelve-hole Wassermann rack, with at least two rows of holes, is filled with three-inch by three-eighths-inch tubes. The front row is for the patient's test, the back row for a control. The tubes in the front row are numbered with a glass marking-pencil, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, and 14. In each tube in the front row, and in the tube in the back row immediately behind it, is placed the number of drops of 0.5 per cent salt solution indicated by the figure marked on the tube in the front row. A capillary pipet drawn from soft glass tubing is used for putting the drops of salt solution in the tubes. With the same pipet distilled water is added drop by drop to each tube, so that there is a total of 25 drops; for example, a tube marked "20" should contain 20 drops of 0.5 per cent sodium chlorid solution and 5 drops of distilled water, and the tube immediately behind it (control tube) should contain the same.

The patient is bled by puncturing the vein in the usual manner for obtaining blood for a Wassermann test. A rather small gage needle should be used, and there should be no delay in getting the blood. An all-glass syringe, sterilized by boiling and thoroughly dried, should be used. It is not necessary to rinse out with normal salt solution; in fact, it would not be advisable, as in this way an excess of salt might be added to the solutions in the tubes. One drop of blood should be allowed to fall into each tube of the front row. The tube should be thoroughly

shaken to make an immediate corpuscle suspension. The plasma is greatly diluted, and usually no fibrin is formed. If a slight clot forms it should be free from corpuscles.

In the back row (control tubes) should be placed blood obtained in a similar manner from a normal person. It may seem unnecessary to use a control in every test. In fact, if several patients are being tested at one time, one control serves for all. The purpose of this test of normal blood is to insure that the salt solution is of the proper strength. Of course, a very slight alteration makes a difference in the result. Ever



Fig. 208. Dilutions are made of 5 per cent sodium chloride solution by adding distilled water to the same method, so that each tube contains 25 drops of hypotonic solution.

patient's blood, then, is considered not only in relation to the different strengths of salt solution determined by reckoning the dilutions in each tube, but also is compared with the behavior of supposedly normal corpuscles in solutions of exactly the same strength.

The tubes are allowed to stand an hour or two at room temperature and the results are then read. The dilution, in which there is just a slight fogging of the supernatant fluid, due to the laking of a few of the least resistant corpuscles, is noted as the point of initial hemolysis. Reading from left to right, the first tube in which it can be demonstrated

that the hemoglobin is entirely free, and that there is no corpuscular residue evident by shaking the tube, indicates the point of complete hemolysis. The percentages of salt solution indicative of initial and complete hemolysis are readily reckoned; that is:

Tube marked 20 showing beginning hemolysis contains  $\frac{2}{3}$  of 0.5 per cent sodium chlorid = 0.40 per cent sodium chlorid.

Tube marked 16 showing complete hemolysis contains  $\frac{1}{2}$  of 0.5 per cent sodium chlorid = 0.32 per cent sodium chlorid.



Fig. 209.—One drop of whole blood is added to each tube of hypotonic solution.

The percentage can be immediately determined by multiplying the number on the tube by 0.02. Normal blood shows beginning hemolysis in 0.42 per cent to 0.38 per cent sodium chlorid solutions and hemolysis to be complete in solutions of 0.36 per cent to 0.32 per cent sodium chlorid. When initial and complete hemolysis occur in solutions stronger than normal, an "increase of fragility" is present. When hemolysis occurs only in solutions weaker than those which lake normal blood, the cells under observation are more resistant than normal and such blood is reported as having an "increase of resistance."

It seems to us important to use chiefly the expressions "initial hemolysis," "complete hemolysis," "increase of fragility," and "increase of



resistance" in order to obviate the confusion of terms which is apt to occur in a discussion of this subject.

### CLINICAL RESULTS

We have had an opportunity to study a comparatively large group of cases of hemolytic jaundice, pernicious anemia, splenic anemia, and myelocytic leukemia with respect to fragility, and the results, although largely of corroborative value, demonstrate certain interesting details.

TABLE 1.—FRAGILITY TESTS IN HEMOLYTIC JAUNDICE  
23 NON-OPERATIVE AND PREOPERATIVE CASES

CASE	PERCENTAGE NaCl				REMARKS
	Initial Hemolysis		Complete Hemolysis		
	Control	Patient	Control	Patient	
86218.....	..	..	.42	.46	..
135948.....	..	..	.34	.40	..
141268.....	..	..	.34	.40	..
153245.....	..	..	.38	.46	..
148209.....	..	..	.36	.40	Brother complete .42.
.....	..	..	.42	.44	..
161538.....	..	..	.38	.44	..
162670.....	..	..	.36	.40	..
94675.....	..	..	.38	.44	..
91298.....	..	..	.32	.40	..
.....	..	..	.36	.40	..
153653.....	..	..	.36	.42	Mother complete at .40. No oper.
157525.....	..	..	.35	.38	Mother complete at .42. No oper.
169405.....	..	..	.36	.42	No operation.
172287.....	..	..	.38	.42	Mild. No operation.
.....	..	..	.36	.42	..
216019.....	..	..	..	.44	No operation.
205552.....	..	..	.36	.42	Father .46—.40.
.....	..	..	.38	.40	..
.....	.44	.46	.36	.38	..
187817.....	.46	.50	.38	.46	No operation.
216591.....	.42	.46	.34	.38	..
192817.....	.44	.50	.36	.42	..
211816.....	.42	.48	.34	.40	..
212273.....	..	.50	..	.40	Father .50—.42.
190364.....	..	.46	..	.40	..
190774.....	..	.50	..	.38	..
.....	.44	.50	.34	.40	..
212934.....	.46	.42	.36	.36	..
Averages.....	.44	.478	.363	.412	

TABLE 2.—FRAGILITY TESTS IN HEMOLYTIC JAUNDICE AFTER SPLENECTOMY (12 CASES)

CASE	PERCENTAGE NaCl				TIME AFTER SPLENECTOMY
	Initial Hemolysis		Complete Hemolysis		
	Control	Patient	Control	Patient	
112836.....	..	..	.34	.40	1 yr. 8 mos.
.....	..	..	.36	.48	1 yr. 9 mos.
141268.....	..	..	.36	.46	18 days
142074.....	..	..	.38	.42	15 days
153245.....	..	..	.34	.42	1 mo.
148209.....	..	..	.36	.36	23 days
.....	..	..	.36	.40	4 mos.
.....	.42	.42	.36	.36	1 yr. 2 mos.
161538.....	..	..	.34	.40	21 days
162670.....	..	..	.32	.42	22 days
.....	..	..	.36	.40	2 mos.
.....	.42	.50	.32	.36	1 yr. 8 mos.
94675.....	..	..	.32	.32	1 mo.
216591.....	.44	.50	.32	.38	22 days
190364.....	.46	.50	.36	.40	18 days
192817.....	.38	.50	.32	.36	24 days
212273.....	.46	.50	.34	.40	19 days
Averages.....	.43	.486	.344	.396	..

TABLE 3.—FRAGILITY TESTS—HEMOLYTIC JAUNDICE

	GENERAL AVERAGES—PERCENTAGE NaCl			
	Initial Hemolysis		Complete Hemolysis	
	Control	Patient	Control	Patient
23 cases non-operative and preoperative..	.44	.478	.363	.412
12 cases postoperative (splenectomy).....	.43	.486	.344	.396
10 cases preoperative.....	.43	.48	.363	.414
Same 10 cases postoperative.....	.43	.486	.34	.39

*Hemolytic jaundice (25 cases, Tables 1, 2, and 3).—*The fragility of erythrocytes has been estimated in 25 patients with hemolytic jaundice. These were all definite cases, although some of them were mild. In 23 non-operative and preoperative cases 29 tests were made; in all but 3 there was a markedly increased fragility. In 2 of these 3 the point of complete hemolysis was 0.02 per cent higher than the controls. In one only of the entire group could the fragility be said to be normal; this was in a very mild but, from all standpoints, a definite case. It is an

important fact that no case which, from a clinical or surgical standpoint, could be diagnosticated as primary hemolytic jaundice, showed an increase of resistance. The fact that hemolytic jaundice may occur with normal fragility is corroborated; but it is possible that observations at other times would show in the same patient an increased fragility. It is also probable that the increased fragility of hemolytic jaundice may be modified by long-continued anemia and by a concurrent septic process, even to the degree that an increase of resistance may be produced.

The relatives of four patients with hemolytic jaundice were found to have an increased fragility—in two instances the father, in one the mother, and in another a brother. Two of these four relatives had no symptoms whatever of the disease, and in two of them the symptoms were first noted at the age of eighteen and twenty years. This would seem to indicate a definite hereditary factor, even in cases in which the onset occurs in later life.

The averages in hemolytic jaundice for initial hemolysis were: controls, 0.44 per cent; patients, 0.478 per cent. The averages for complete hemolysis were: controls, 0.365 per cent; patients, 0.413 per cent. The point of highest initial hemolysis was 0.50 per cent; the point of highest complete hemolysis was 0.46 per cent.

After splenectomy (Table 2) for hemolytic jaundice seventeen tests were made in twelve cases. In general an increased fragility was present in estimations made fifteen days to one year and nine months after splenectomy. There was, however, a definite although slight decrease of fragility with respect to complete hemolysis, although only two patients showed a normal resistance. One patient, who had in all six tests, gave a return to normal for both initial and complete hemolysis one year and two months following operation. The point of initial hemolysis did not, however, show this definite shift toward normal after splenectomy.

The averages after splenectomy for hemolytic jaundice were: for initial hemolysis controls, 0.43 per cent; patients, 0.486 per cent. The averages for complete hemolysis were: controls, 0.344 per cent; patients, 0.396 per cent.

In a total of 260 tests on 225 patients a definite increase in fragility, 0.04 per cent or more, was found in only four cases which were not hemolytic jaundice. This is no greater number than would be accounted for by errors of technic. These cases were, respectively, an acute lymphatic leukemia, a lymphosarcoma, an inoperable carcinoma of the stomach.

and an indefinite case with splenomegaly and arthritis. Increased fragility in cases with cyanosis has been noted by others in a few instances. By these observations the value of the fragility test in the diagnosis of hemolytic jaundice is conversely demonstrated; that is, the finding of a definite increase of fragility is almost certain evidence of the existence of hemolytic jaundice.

Butler has shown that both washed (sodium chlorid) and unwashed corpuscles of patients with hemolytic jaundice show an increased fragility; and that, as with normal cells, oxygen increases their resistance slightly while carbon dioxid increases their fragility. He reports six cases occurring in two families. Davis corroborates the findings with respect to washed corpuscles.

TABLE 4.—FRAGILITY TEST—MYELOCYTIC LEUKEMIA (12 CASES)

CASE	MINIMUM RESISTANCE, CONTROL	MINIMUM RESISTANCE, PATIENT	MAXIMUM RESISTANCE, CONTROL	MAXIMUM RESISTANCE, PATIENT	DATE
173747.....	..	..	.36	.36	10- 2-16
180499.....	..	.46	..	.38	5- 9-17
173740.....	..	..	.36	.36	10- 2-16
221207.....	..	.46	..	.34	2-12-18
194399.....	.44	.42	.36	.34	5-16-17
221664.....	.40	.46	.32	.36	2-11-18
..	.42	.46	.36	.34	2-15-18
173772.....	..	..	..	.34	9-29-16
194933.....	.42	.42	.34	.30	5-23-17
207035.....	.46	.46	.38	.32	9- 6-17
220165.....	.46	.40	.34	.30	2-12-18
..	.42	.44	.36	.34	1-23-18
168742.....	..	..	.34	.34	8-22-16
..	..	..	.36	.28	2- 2-17
192150.....	.34	.38	.30	.30	4-28-17
Averages....	.42	.436	.348	.333	..

*Myelocytic and lymphocytic leukemia.*—The resistance of the erythrocytes is shown to be normal in myelocytic leukemia (12 cases, Table 4). There may be a slight general tendency toward an increase of resistance, but this is not of a definite nature. The averages were: for initial hemolysis controls, 0.42; patients, 0.436; for complete hemolysis controls, 0.348; patients, 0.333. Patients were tested before and after the application of radium over the spleen, and it was thought in two instances that an increased fragility followed the use of radium. This observation did not, however, prove to be constant. Three cases of lymphocytic leukemia were tested, two of them showed normal resistance, and one,

an acute case, a slight increase of fragility. Butler noted normal fragility in two cases of myelemia and one of lymphemia.

*Splenic anemia (14 cases, Table 5).*—The cases of splenic anemia in this group were carefully selected. Identifiable cases of chronic septal splenomegaly, luetic splenomegaly, cirrhosis of the liver, and, so far as possible, all of those diseases which have been so commonly confused with splenic anemia in the literature were excluded. In most of the cases of splenic anemia a definite increased resistance was shown. The averages for the fourteen cases were: for initial hemolysis controls, 0.438; patients, 0.402. Complete hemolysis controls, 0.353; patients, 0.316, with an average hemoglobin of 44 per cent. There seemed to be a still more definite increase of resistance following splenectomy.

TABLE 5.—FRAGILITY TEST IN SPLENIC ANEMIA (14 CASES)

CASE	PERCENTAGE NaCl				Hb	RES. BLOOD CELLS X MILLION
	Initial Hemolysis		Complete Hemolysis			
	Control	Patient	Control	Patient		
224466 .....	.40	.44	.34	.36	52	3.16
161083 .....	..	..	.36	.36	50	4.54
165779 .....	..	..	.34	.34	34	3.46
158085 .....	..	..	.36	.36	45	3.33
214034 .....	.44	.38	.38	.30	52	3.26
.....	..	.38	..	.28	..	..
167319 .....	..	..	.30	.30	73	4.91
216004 .....	..	.42	..	.32	38	2.57
214146 .....	.42	.40	.34	.30	26	2.38
144914 .....	.42	.42	.34	.34	63	3.32
215670 .....	.46	.42	.36	.34	15	1.57
191277 .....	.44	.44	.36	.30	62	3.96
.....	.42	.40	.34	.28—	45	3.77
209234 .....	.48	.42	.38	.32	20	2.54
119565 .....	.44	.30	.38	.28—	30	2.06
129358 .....	.46	.40	.36	.28	60	4.3
Averages .....	.438	.402	.353	.316	.443	3.25

Karsner and Pearce have demonstrated an increase of resistance experimentally following splenectomy in animals; it occurred in association with the anemia, apparently due to splenectomy. The increase in resistance following splenectomy for splenic anemia in man occurs without apparent relationship to the already existent anemia. One patient showed complete hemolysis, less than 0.28 per cent, two years and ten months after operation. The increased resistance in cases of splenic

anemia preceding splenectomy may be entirely secondary to the chronic anemia. There is, however, a similarity to the increased resistance of cases of portal cirrhosis in which anemia of a definite degree has never been present. Hill found normal fragility in two cases of splenic anemia.

*Pernicious anemia (18 cases, Table 6).*—Although pernicious anemia has certain features that are similar to hemolytic jaundice, there is no similarity in the behavior of the erythrocytes to hypotonic salt solution. The resistance of the red cells is usually definitely increased in pernicious anemia, although in some of the cases it is normal. The averages for eighteen cases were: for initial hemolysis controls, 0.428; patients, 0.408; complete hemolysis controls, 0.355; patients, 0.322, with the hemoglobin averaging 45 per cent and the red cell count 2,280,000. It is possible that the increase of resistance has been due to the chronic anemia present.

TABLE 6.—FRAGILITY TEST IN PERNICIOUS ANEMIA (18 CASES)

CASE	PERCENTAGE NaCl				Hb	RED BLOOD-CELLS IN MILLIONS	TIME AFTER SPLENECTOMY
	Initial Hemolysis		Complete Hemolysis				
	Control	Patient	Control	Patient			
188649....	.44	.40	.36	.32	55	2.49	..
212480....	.44	.38	.38	.34	33	1.33	..
139695....	..	..	.36	.28	30	1.78	7 mos.
158136....	..	..	.36	.30	28	1.51	7 wks.
162242....	..	..	.34	.24	50	1.9	..
220132....	.42	.40	.36	.32	43	1.67	..
151088....	..	..	.36	.30	41	1.98	4 mos.
153395....	..	..	.32	.30	75	3.81	3 mos.
157290....	..	..	.32	.30	84	5.2	18 days
188717....	..	..	.33	.36	30	1.31	..
197254....	.42	.42	.36	.36	40	1.51	..
181414....	..	..	.36	.36	19	1.03	..
160970....	..	..	.38	.32	50	2.57	..
170115....	..	..	.36	.36	39	2.44	..
129968....	..	..	..	.32	71	2.6	3 wks.
164775....	..	..	.34	.34	29	1.9	..
196267....	.42	.44	.32	.34	33	1.74	..
124257....	..	..	.38	.34	68	4.28	3 mos.
Averages	.428	.408	.355	.322	.454	2.28	

Again, as with splenic anemia, the resistance of erythrocytes is increased quite definitely after splenectomy. This fact, I believe, has not been previously shown so clearly in any other series of cases.

Hill, using washed corpuscles, found that fragility in thirteen cases

of pernicious anemia was either high, low, or normal, while Davis's findings more nearly agree with ours in that they demonstrate usually increased resistance.

TABLE 7.—FRAGILITY TESTS IN PURPURA (4 CASES)

CASE	PERCENTAGE NaCl			
	Initial Hemolysis		Complete Hemolysis	
	Control	Patient	Control	Patient
12155.....	.46	.46	.34	.34
212138.....	.46	.44	.36	.36
214778.....	.42	.42	.34	.34
228359.....	.40	.40	.32	.32
Averages.....	.435	.43	.34	.34

*Purpura (4 cases, Table 7).*—Fragility tests in four patients with severe forms of purpura demonstrate normal values. There is no variation whatever from normal, and although the series is small, the results are sufficiently definite to be indicative. Butler obtained normal readings in one case of purpura.

TABLE 8.—FRAGILITY IN ANEMIA OF SECONDARY TYPE (11 CASES)

CASE	PERCENTAGE NaCl				Hb	RED BLOOD-CELLS IN MILLIONS	REMARKS
	Initial Hemolysis		Complete Hemolysis				
	Control	Patient	Control	Patient			
212144.....	..	.42	..	.34	45	3.99	Colitis
156102.....	..	..	.34	.28	29	3.68	Uter
221504.....	.44	.40	.36	.28	30	3.71	Ovarian
179009.....	..	..	.38	.30	28	2.6	Cellulitis
166483.....	..	..	.32	.32	39	3.52	Myoma
162653.....	..	..	.34	.24	29	2.38	Hemorrhage
210376.....	.46	.46	.38	.30	42	4.0	Hemorrhage
195342.....	.42	.42	.32	.28	35	3.04	Colitis
159417.....	..	..	.34	.34	38	3.99	Myoma
208004.....	.44	.44	.36	.34	37	3.56	Hematuria
221439.....	.38	.40	.34	.32	48	2.97	Sepsis
Averages.....	.425	.424	.349	.308	38.3	3.503	

*Severe anemia of secondary type (11 cases, Table 8).*—Anemia of low color index, whether due to hemorrhage or a chronic infectious process

is most apt to be associated with an increased resistance of the erythrocytes. Normal resistance is seen in some instances, but the averages show a fall of 0.04 per cent for complete hemolysis. The degree of anemia bears a relationship in most of the cases to the increase of resistance. The readings are quite comparable to those of pernicious anemia. Similar conclusions were drawn by Hill.

TABLE 9.—FRAGILITY TEST IN CHRONIC OBSTRUCTIVE JAUNDICE  
(12 CASES)

CASE	PERCENTAGE NaCl				REMARKS
	Initial Hemolysis		Complete Hemolysis		
	Control	Patient	Control	Patient	
206433.....	.40	.40	.32	.32	No operation; probable cancer, gallbladder and chronic jaundice (3).
157154.....	..	..	.30	.30	Stone common duct, jaundice (3) three months.
167420.....	..	..	.32	.32	Biliary cirrhosis, splenectomy, jaundice (3).
189394.....	.46	.42	.36	.32	Stones, gallbladder, pancreatitis, cirrhosis, jaundice (2).
156252.....	..	..	.36	.28	Cirrhosis of liver, ascites, jaundice (2), one year.
170914.....	..	..	.36	.28	Chronic pancreatitis common duct, obstructive jaundice (3), six weeks.
217651.....	.42	.36	.36	.18	Carcinoma? pancreas. Jaundice. (2), one month.
223891.....	.42	.38	.32	.28	Sandy muddy material common duct, jaundice (2).
180780.....	..	..	.32	.28	Subacute pancreatitis, cancer? Hypertrophic cirrhosis.
192980.....	.44	.42	.36	.28	Stones in gallbladder, suppurative cholangitis, pruritus.
210429.....	.48	.40	.38	.28	Traum. strict. common duct, complete closure, jaundice.
201168.....	..	..	..	— .28	No operation, jaundice (2) one year, gallbladder, enlarged liver.
Averages.	.436	.396	.342	.31	

*Chronic obstructive jaundice (12 cases, Table 9).—*The averages obtained in cases with chronic jaundice of the obstructive type are, for initial hemolysis, 0.396 per cent, and for complete hemolysis, 0.31 per cent. A definite increase in resistance is demonstrated. Certain cases of chronic obstructive jaundice give approximately normal readings, but in the large majority of instances resistance is markedly increased.



Whether this is due entirely to the jaundice or also to factors present as a result of complications cannot be determined. There is no reason to conclude that chronic septic and toxic processes, as well as bile-pigments, increase the resistance of erythrocytes, and it is probable that cirrhosis of the liver, pancreatitis, and gallbladder and duct infections, as well as the jaundice itself, may be factors affecting corpuscle resistance. Ribierre's thesis contains a most interesting study of factors affecting fragility in obstructive jaundice. Subsequent observations have corroborated his clinical findings.

TABLE 10.—FRAGILITY OF ERYTHROCYTES

	NUMBER CASES	PERCENTAGE NaCl			
		Averages		Averages	
		Initial Hemolysis		Complete Hemolysis	
		Control	Patient	Control	Patient
Hemolytic jaundice (non-operative and preoperative) . . . . .	23	.44	.478	.363	.412
Hemolytic jaundice (after splenectomy) . . . . .	12	.43	.486	.344	.396
Myelocytic leukemia . . . . .	12	.42	.436	.348	.383
Splenic anemia . . . . .	14	.438	.402	.353	.316
Pernicious anemia . . . . .	18	.428	.408	.355	.322
Purpura . . . . .	4	.435	.43	.34	.34
Secondary anemia . . . . .	11	.425	.424	.349	.304
Chronic obstructive jaundice . . . . .	12	.436	.396	.342	.31

We have not reported in this paper the results on a large number of miscellaneous cases. Conclusions may be drawn only when a group of cases has been studied; isolated findings may be misleading (Table 10).

#### SUMMARY

A total of 260 tests in 225 cases is the basis for this report. A modified and somewhat simplified Ribierre method has been used.

1. Twenty-five patients with hemolytic jaundice were examined. In all but three there was a markedly increased fragility. Two of these three showed an increased fragility of 0.02 per cent. In only one could the resistance be said to be normal. Of the entire group of 225 cases there were only four with definitely increased fragility in which a diagnosis of hemolytic jaundice could not be made. Relatives of four pa-

tients with hemolytic jaundice were found to have an increased fragility; two of these four relatives had no symptoms of the disease, and in the patients themselves the onset of the disease dated to the age of eighteen or twenty years, indicating a hereditary factor even though the onset was late. After splenectomy there was found a slight decrease in the degree of fragility, especially with respect to initial hemolysis.

2. Twelve cases of myelocytic leukemia showed normal fragility with very slight variations toward increased resistance.

3. In fourteen cases of splenic anemia, excluding as far as possible all those conditions so commonly confused with splenic anemia, a definitely increased resistance of erythrocytes was shown. A yet greater increase of resistance was demonstrated after splenectomy.

4. In pernicious anemia (18 cases) the resistance of erythrocytes was slightly increased. Here again, after splenectomy, there was a more definite increase of resistance.

5. Four cases of severe purpura showed a strikingly normal hemolysis without variations.

6. Anemia of low color index, whether due to hemorrhage or to chronic sepsis, was accompanied by an increase of resistance.

7. In eleven cases of chronic obstructive jaundice in general an increase of resistance was shown.

The test for fragility of erythrocytes in hypotonic salt solution is of definite practical value, especially in the diagnosis of all those diseases which may simulate hemolytic jaundice. It is more accurate when compared with a control test of normal blood.

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## A MODIFICATION OF THE MOSS METHOD OF DETERMINING ISOHEMAGGLUTINATION GROUPS\*

A. H. SANFORD

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It is well known that the iso-agglutinins in human serum are thermostabile, and it occurred to me that agglutinating properties in human serum might be easily preserved by drying. The experiment was made as follows to determine this point: Cover-slips were cleaned and dried. On several of these were placed two loopfuls of serum from persons of Group III. In like manner cover-slips were prepared with serum from Group II persons. These droplets of serum were allowed to dry in the air, and were then wrapped in paper and placed in the ice-box. After more than two months they still possessed marked agglutinating properties. To demonstrate this, one loopful of corpuscle suspension of a Group II person was used to dissolve the dried Group III serum on one of the cover-slips. When this was inverted over the concavity on a hanging-drop slide, it was noted that agglutination of the cells occurred almost immediately, as in the Brem method. When the corpuscle suspension of the same group as the serum was used to dissolve the dried material on the cover-slip, no agglutination occurred. Since we are asked from time to time to send known serums to laboratory workers who contemplate using either the Moss or the Brem method for determining groups in the selection of donors for transfusions, it would seem that this method of using dried serum could well be employed in two ways:

1. The group in which a patient belongs might be determined by preparing several cover-slips with serum of the person to be tested. These could be sent to a laboratory equipped to make the necessary tests, and by dissolving the dried serum with corpuscle suspension of a known group the patient's group would be readily determined. The technic is to dissolve the serum on one cover-slip with one or two loop-

\* Reprinted from Jour. Am. Med. Assn., 1918, lxx, 1221.

f suspension of Group II corpuscles made by allowing two or three of blood from a Group II person to fall into 1 c.c. of 2 per cent m citrate solution. Another cover-slip preparation may be made

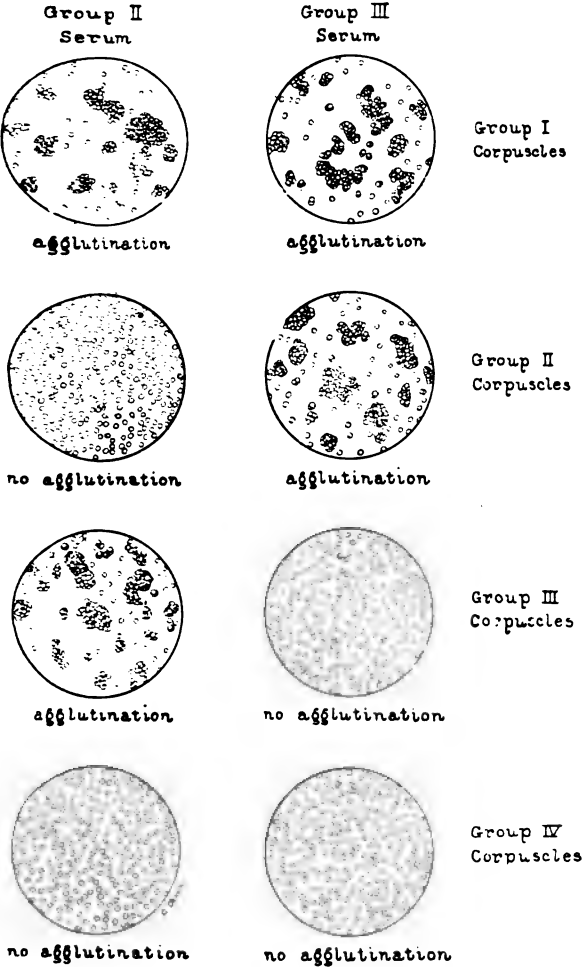


Fig. 210.—Appearance of hanging-drop preparations of corpuscle suspensions of four different groups (Moss classification) used to dissolve Group II and Group III serum dried on cover-slips.

by dissolving the serum from a loopful of Group III corpuscle suspension. Hanging-drop preparations are then made and examined under the microscope. Agglutination of corpuscles on both slides places the unknown serum in Group IV. No agglutination after ten minutes on either

slide places the unknown serum in Group I. Agglutination of the Group III corpuscles and no agglutination of the Group II corpuscles place the unknown in Group II, and agglutination of the Group II corpuscles and no agglutination of the Group III corpuscles place the unknown in the reciprocal Group III.

2. This method may be used very well by laboratory workers who desire to start grouping unknown blood and who must have known serum for beginning these tests. The technic is to collect from the unknown person a few drops of blood in 1 c.c. of 2 per cent sodium citrate solution to make a corpuscle suspension similar to the method described by Brown.

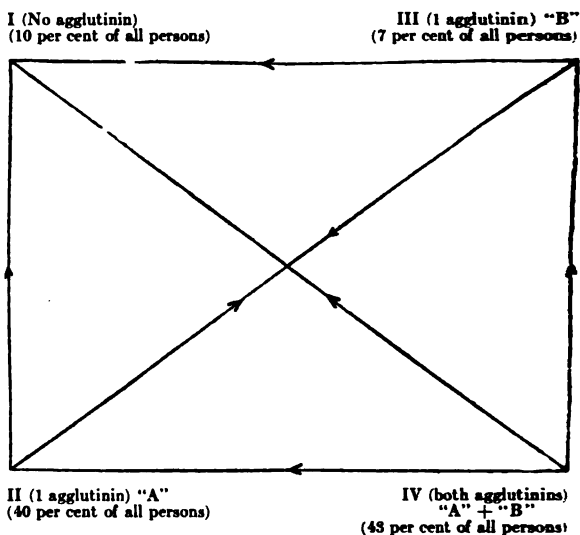


Fig. 211.—Moss agglutination groups: The corpuscles of the various groups are agglutinated by the serum of the groups from which the arrows lead.

One or two loopfuls of unknown corpuscle suspension is used to dissolve the Group II serum dried on the cover-slip marked known Group II serum. In like manner a drop of the corpuscle suspension is used to dissolve the dried Group III serum. Hanging-drop preparations are made and examined in the usual manner. Agglutination on both of the slides will place the unknown blood in Group I. No agglutination on either of the slides after ten minutes will place the persons in Group IV. Agglutination of the unknown corpuscles with Group III serum and not with Group II will place the unknown in Group II and vice versa. Group III blood is demonstrated by agglutination with the Group II serum and no agglutination on the other side. Reference to the diagram

the relation of the agglutination groups to each other (Fig. 211) be helpful in following the technic of this test.

I am prepared to send serums to laboratory workers interested in determination of iso-agglutination in connection with the selection of donors for transfusion.<sup>3</sup>

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previous to this. Blundell exposed the femoral artery and vein of a dog and introduced a pipe into each. The blood was allowed to flow from the artery into the cup, and was then reinjected into the vein by means of a syringe. This was continued for a period of twenty-four hours, about twelve pints of blood in all being reinjected. The dog lived. Later he transfused women suffering from loss of blood due to childbirth, employing human blood, and it is recorded that three out of seven attempts were successful.

In 1835 Bischoff introduced the idea of injecting defibrinated blood, and this method became popular with a large group of workers, among whom were included Prevost, Panum, Dieffenbach, and Brown-Séguard. While it was pointed out by Köhler in 1877 that this form of transfusion was fraught with danger, owing to the excess of fibrin ferment injected, and its use was discouraged by Landois, Gesellius, Ponfick, and others, it was used throughout the nineteenth century, although with somewhat abated enthusiasm, and in fact was quite extensively employed during the first decade of this century, until it was replaced by the simple methods of today (Moss, Brem, and Lichtenstein). During this period other methods were devised. Higginson and Aveling used two cannulas attached by tubing to a bulb syringe. Gesellius and Leisrink, in 1872, employed a glass cannula, and Landois, in 1875, transfused directly from vein to vein, employing cannulas and tubing. Phosphate of soda (Braxton Hicks) and minute quantities of ammonia (Richardson) were advocated as anti-coagulants.

Transfusion became an established procedure the latter part of the nineteenth century, and was practised with a considerable degree of frequency. The success attending the operation was at times brilliant, but reactions described as oppressed breathing, choking, and a train of other more or less serious symptoms, met during transfusion, were likely to be attributed to the accidental entrance of air into the vein, although as early as 1818 Blundell showed experimentally that the admission into the veins of a small amount of air did not produce any serious effect on the animal. Oré showed that a large quantity of air allowed to enter the veins resulted in death, but minute quantities, as might accidentally get into them, produced no ill effects. This was also observed by Löwenthal in 1871. In the light of our present knowledge it is certain that many of these were the result of incompatible bloods.

Professor Martin, of Berlin, in 1859, published reports of 57 cases in which transfusion was done in obstetric practice. There were suc-

cessful results in 43. Blasius, in 1863, collected all the cases for forty years previous, and recorded 116, 56 of which were successful. It is interesting to note that 14 of these in which undefibrinated blood was used all proved unsuccessful. In the main, clinical indications for transfusion were then recognized similar to those which are observed today. Leisrink, in 1872, says: "Transfusion is indicated in all those pathologic conditions where the blood, in quantity and quality, is so altered that it is unfit to fulfil its physiologic duties." Fryer, who apparently was the first in this country to employ transfusion, and who used a modified Aveling apparatus, consisting of tube, bulb, and cannulas, recommended its use in asthenic patients before and after necessary surgical measures in order to avert pyemia and its allied evils, especially in operations in which the peritoneum is involved (Fig. 213). Dumas and Prevost and Landois pointed out the injurious effects of transfusing the bloods of dissimilar species. Brunton, Hüter, and Gesellius, in 1870 to 1873, advocated its use in case of monoxid poisoning and reported successfully treated cases. Judging from the frequent warning against its use in bleeding cases, except after the bleeding point had been checked, it is evident that its hemostatic effect was not recognized.

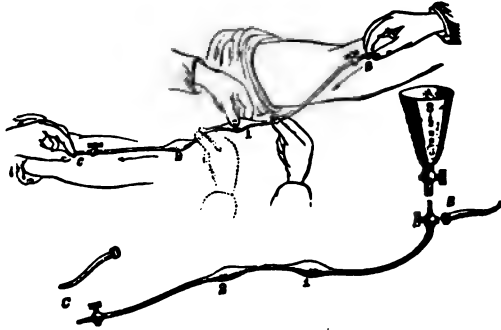


Fig. 213.—Transfusion apparatus (taken from Fryer).

Buchser, in 1869, reports a case of a young woman, almost exsanguinated from bleeding from the vagina and bladder following convalescence from typhus, who was transfused with three ounces of blood from her husband by letting the blood run into a warmed receptacle and then injecting it with a syringe into the recipient, which resulted in cessation of the bleeding.

Smith, in 1873, reported the case of a child, aged eight years, with purpura, who had bled from the nose until practically exsanguinated, and was then transfused by means of syringe and cannula, defibrinated blood being employed. The result was excellent. No mention was made of the idea of hemostasis, and it is apparent that the transfusion was employed solely with the view of replacing lost blood. Its value following



hemorrhage was early appreciated. Hicks attributes its want of success in these cases to the postponement of the operation until too late. He recognized that patients who had suddenly lost a large amount of blood were less likely to respond than those whose exsanguination had been protracted.

Autotransfusion by the application of Esmarch bandages to the extremities was advocated by Lesser in 1875.

In 1875, with the introduction of normal saline solution for intravenous therapy, there again followed a period of about thirty years in which there was a very noticeable decline in the enthusiasm for the employment of, blood transfusion. Because of the technical difficulties met in the successful employment of the technic in use at that time and because, also, of the varied results achieved, owing, doubtless, to the want of the proper understanding of iso-agglutination and isohemolysis, saline infusion was quickly adopted as a substitute. Prior to this, in 1850, Hodder, in Canada, reported cases of cholera treated successfully by the intravenous injection of fresh cow's milk, and Brinton, lecturer at the Jefferson Medical College in 1878, basing his opinion on the reports of Hodder, Thomas, and others, advocated the injection of milk in place of blood transfusion. He concluded that it was feasible and safe, that it was easier than blood transfusion, that it was commonly followed by chills, that the dosage should not be over eight ounces, and that its practice should not be limited to patients prostrated from the loss of blood, but should be employed in disorders which greatly deplete the blood, as in cholera, pernicious anemia, typhoid fever, and others.

While the operation made rapid advances during the nineteenth century, there were two important factors which greatly impeded its progress, that is, the tendency for the rapid clotting of blood during its transference from the donor to the recipient, and the occurrence of hemolysis resulting from the employment of incompatible bloods. To overcome the first of these, ingenious apparatuses for the rapid transference of the blood were devised, defibrinated blood was employed, and attempts were made to delay the coagulation by the addition of chemicals. These were only partially successful. During this time knowledge of iso-agglutination and isohemolysis was lacking, although its clinical occurrence was seen often and repeatedly described in reports, but the symptoms resulting were attributed to the introduction of air into the veins.

Early after the advent of the present century rapid progress was made in meeting and overcoming the two chief dangers associated with blood transfusion. Landsteiner and Shattuck independently reported the presence of iso-agglutinin, and Landsteiner, in 1901, divided human beings into three groups according to the agglutinating reactions of their bloods. In 1907 Jansky proved that human beings fall into four groups and this was later confirmed by Moss, who made the important observation that hemolysis of the red blood-cells never occurs without their previous agglutination. The tests for the group determination were simplified by Brem, Sanford, and others.

Great strides in blood-vessel surgery were being made at this time, notably by the work of Murphy in 1897, Dörfler in 1899, Carrel and Guthrie, Crile, and others, and this lent impetus to the development of more certain methods of transferring blood.

The first permanent suture of blood-vessels was made by Eck, a Russian, in 1879, when he established a lateral anastomosis between the portal vein and the inferior vena cava. Murphy, in 1897, successfully anastomosed in man the divided femoral artery by invaginat-

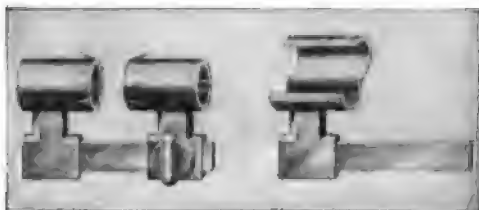


Fig. 214.—The complete Soresi instrument; the figure on the right shows how the instrument opens on a hinge (taken from Soresi).

ing the proximal into the distal end. Carrel and Guthrie, by the most painstaking details, perfected blood-vessel suture. While Nitze, in 1897, and Payr, in 1900, made successful vessel anastomoses by means of ivory clamps and magnesium rings, respectively, it remained for Crile, the real pioneer in modern blood transfusion, to perfect a method of anastomosing vessels, intima to intima, by the employment of a cleverly devised cannula. He put the method in practice experimentally, and in clinical research, reporting 225 experimental and 32 clinical transfusions, at first anastomosing artery to vein, and later showing that transfusion could be successfully and more readily accomplished by vein to vein anastomosis.

Stimulated by this work, the profession began to realize more clearly than ever the really enormous therapeutic value offered by blood transfusion, and there followed in rapid succession the publication of numerous articles describing "new and simple" methods for transferring blood and

advocating wider fields of application. In 1909 Brewer and Leary, after successfully experimenting on 31 animals, advocated transfusion by the interpolation between the artery and vein of a paraffin-coated glass tube. In the same year Frank and Baehr transfused by means of a vascular bridge or link made from a dog's carotid and preserved in 2 per cent formalin, to connect the artery to the vein. The Lespinasse and other modifications followed.

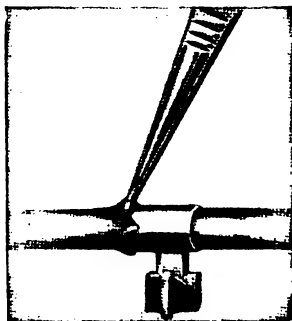


Fig. 215.—Showing how the blood-vessel is cuffed over the hooks while the blood is still flowing in it; the dotted line shows where the vessel must be cut (taken from Soresi).

Ingenious modifications of the Cline formula were devised by Buerger, Soresi, Jassway, McGrath, and others (Figs. 214 and 215).

Hull has described a method of arteriovenous anastomosis, which, for its simplicity

and sureness of accomplishment, should commend itself to those who may have occasion to perform an emergency transfusion, when antiseptics, coagulants and the ordinary apparatuses are not to be obtained. The donor's radial artery is exposed and divided, and compression is made on its proximal end to prevent flowing. The recipient's vein is exposed for a distance of one inch and a small slit is made in it, large enough to admit the artery, which is carried into it by means of a needle and suture (Fig. 216). Mann has reported its successful application in experimenting with the method in the laboratory.



Fig. 216. A simple arteriovenous anastomosis (according to Hull).

The use of any of these methods necessitated the sacrifice by the donor of either an artery or a vein, and with every donation he subjected

himself to considerable risk. In addition it was impossible accurately to determine the amount of blood transfused, estimates being based on blood-pressure and hemoglobin readings. Curtis and David overcame the last objection by employing a receptacle for the blood and then reinjecting. Their apparatus consisted of a glass bulb, paraffin coated, with two cannula tips at one end and attached to the other end by means of rubber tubing, a syringe. This idea was modified by Kimpton and Brown, Percy, and Satterlee and Hooker, and it resulted in the perfection of a method of transfusion which, under favorable circumstances, is ideal. The one essential objection lies in the difficulty in the coating of the tube and connections with a uniform layer of paraffin. Any error in this means failure.

In 1892 von Ziemssen devised and employed successfully a method of transfusion by means of syringes and cannulas: "By rapid work he was able to draw 20 c.c. of blood from a subcutaneous venous puncture, disconnect the syringe, and empty it through a needle similarly placed in the recipient's vein before coagulation took place. By filling the syringes one after another he transfused 280 c.c. at one time." The method did not receive the attention it deserved and was soon forgotten.

In 1913 Lindeman improved the technic by adding a larger number of syringes which were kept constantly washed by an assistant. He devised a special nest of three cannulas, the outer one rounded on its end to prevent injury to the intima. The technic was certain and, with a specially trained operator and assistants, the method was nearly perfect. By the utilization of the principle of a two-way stop-cock, modifications were devised by Freund, Unger, and Kush.

In 1914 Hartwell wrote: "The attainment of the ideal seems to lie in the development of a method by which coagulation and other alterations of the blood are prevented during the time required to draw sufficient blood (1000 c.c.) into a receptacle connected by subcutaneous venous puncture with the donor and to empty it again through a similar puncture in the recipient—these two principles, if desirable, being in separate rooms." Except in the hands of those skilled in the application of a special technic, and under the most favorable circumstances, none of the methods up to this time fulfilled all these requirements. Excluding those methods in which the technic required the employment of a paraffin-coated receptacle, the successful application of all others was dependent on the rapid transference of blood from donor to recipient in less than the normal coagulation time. In devising a technic

to fulfil the requirements of the ideal, it was natural then that no should be sought to retard the coagulation time without altering normal properties of the blood. Various means were employed, that by the dilution of the blood with normal saline, by isotonic glucose and by the addition of chemicals, namely, hirudin and sodium citrate.

In 1914 and 1915 Hustin, Agote, Weil, Lewisohn, Rueck, and others working independently of one another, published articles recording experiments, and clinical application of transfusions performed with citrated blood. Hustin's article appeared Aug. 6, 1914. He mixed blood with equal parts of isotonic (5 per cent) glucose solution to which was added 20 c.c. of sodium citrate for every 200 c.c. of blood-glucose mixture. He claimed that citrate of soda impaired the oxygenating property of the blood, and the addition of glucose was necessary to overcome this. He reported experiments and one clinical application in man. The first transfusion performed in man by blood rendered incoagulable by the addition of sodium citrate alone was performed by Prof. L. Agote, of Buenos Aires, on Nov. 14, 1914. He employed 1 grain of neutral sodium citrate in 25 per cent solution for every 100 c.c. of blood. Weil observed that citrated blood augmented the coagulative properties of the recipient's blood. From the work of Lewisohn in determining the proper dosage of sodium citrate which can be used with safety there has developed a method which "unites four advantages in surgery of extreme importance—facility, rapidity, efficacy, and security," and which fulfills in every detail the requirements of the ideal.

#### CLINICAL APPLICATION

This report of a series of 1036 blood transfusions, summarizing the results and recording the general indications and dangers, is submitted because of the belief that the most accurate test of the value of any therapeutic procedure, developed from experimental study, lies in its repeated clinical application.

The 1036 transfusions were performed on 429 patients between Jan. 1, 1915, and Jan. 1, 1918, in the Mayo Clinic. Five were done by means of the paraffin-lined cylinder, 30 by a modified cannula-syringe technic, and the others, 1001, by the citrate method.

#### INDICATIONS FOR TRANSFUSION

With the development of simpler methods of technic, and with the introduction of accurate blood tests, blood transfusion has lost the dan-

which once attended its use, until today it is a safe and proved therapeutic measure, rather than merely a means of last resort. If blood transfusion is looked on as a homologous transplantation of living tissue, as suggested by Hartwell, the indications may be epitomized as being those which indicate the necessity of restoring the lost or impaired body tissue (blood) by a homologous transplant. Definite effects of transfused blood are: (1) Restoration of the bulk of the circulating fluid; (2) provision of oxygen and assimilable pabulum for tissues; (3) increase of the coagulability; (4) stimulation of the hematopoietic organs, and (5) increase of resistance to infection by its antitoxic and bactericidal properties.

In this series the cases may be grouped according to indications for transfusion as follows:

1. Primary (pernicious) anemia, 657 transfusions in 185 cases.
2. Secondary anemia, 243 transfusions in 149 cases.

Chronic infection.....	24 cases
Malignancy.....	44 cases
Chronic hemorrhages.....	43 cases
Acute hemorrhages.....	7 cases
Hemolytic jaundice.....	4 cases
Splenic anemia.....	10 cases
Actinomycosis.....	2 cases
Causes unknown.....	15 cases

3. Bleeding, 81 transfusions in 59 cases.
4. Acute toxic and septic conditions, 34 transfusions in 25 cases.
5. Leukemias, 20 transfusions in 10 cases.
6. Shock, 1 transfusion in 1 case.

A detailed analysis will not be made of the cases included in this report, but for completeness a general summary and discussion of the results obtained will be given under each group of cases.

*Group I. Pernicious anemia.*—Basing his opinion, presumably, on the fact that destruction of the patient's own blood is more or less continuous in this group of cases, Soresi classified pernicious anemia with malignancy, as being the two diseases in which the operation for blood transfusion was absolutely contraindicated. While the percentage of occurrence of the milder reactions following transfusion is decidedly greater in this class of cases, due probably to the slight hemolytic action of the blood of the patient on the blood transfused, definite beneficial effects are seen in a very large percentage of cases. The result varies in different patients, and also in the same patient, following separate transfusions. Whether this variation is the result of the difference in

the stimulating properties of the bloods of the different donors, or to a difference of degree in the active hemolysis of the patient, depending on the stage of the disease, is a matter of conjecture. The observation based on the results in this series would tend to support the latter theory. One patient who had been transfused previously, with definite improvement, returned after several months in a very grave condition—lethargy, temperature  $102^{\circ}$  to  $103^{\circ}$ , hemoglobin below 20, and red blood-cells below 1,000,000. He was given 500 c.c. of blood from a suitable donor. A definite reaction of chill, fever, increased drowsiness, and hemoglobinuria followed, and later, herpes on the lip. The patient received no improvement from the transfusion.

A series of transfusions ranging from 1 to 30 was practised in the cases in this group; some were performed preceding and following splenectomy, but the vast proportion were in non-operated cases. The results were equally good in the different groups. One case of unusual interest is herein reported:

A male, aged thirty-six years, was admitted for examination Feb. 10, 1915, with a history of good health until about one year previous to admission, when weakness, shortness of breath, and increasing pallor gradually developed. From the history, examination, and blood findings a diagnosis of pernicious anemia was made. At this time his hemoglobin was 20 per cent, red blood-cells 1,730,000, with the presence of normoblasts and megaloblasts. Splenectomy was performed March 10, 1915, and April 7, 1915, before his dismissal, the hemoglobin was 70 and the red cells 3,640,000. Following acute tonsillitis in the fall he began to run down, and Dec. 1, 1915, he returned with hemoglobin 20, and red blood-cells 1,190,000. From then until May, 1918, he had 35 transfusions of 500 to 750 c.c. each. His response to the transfusions has been remarkable. Ordinarily two to four transfusions at weekly intervals are required to effect a definite remission in the course of disease. His condition now is apparently as good as it was two years previously. It is of special interest to note that the blood of the patient belongs to Group I, and while there has been transfused into him blood of all four groups, without any evidence of hemolysis, he has retained his original grouping.

The conclusions of Archibald, who made an extensive study of a part of the cases in this series, holds good for the series in its entirety. In effect his conclusions were that the greater number of the patients, except those who have reached the very last stages of disease, will receive immediate benefit from the transfusion of blood. Many also

who are in extremis, and who are not benefited by medical treatment alone, will show great improvement by a series of blood transfusions.

*Group 2. Secondary anemias.*—Except in the seven instances in which the anemia was owing to acute hemorrhage, the majority of the patients in this group were transfused preliminary to operation, with the idea of improving their general condition and thereby increasing their resistance to infection. In cases of acute, frank, and concealed hemorrhages, the enormous value of replacing the lost bulk of fluid by blood in connection with efficient surgical means of checking further loss is well recognized. As pointed out by Hicks in 1869, “the want of success in transfusion lies in the postponement of the operation until too late a period.” The normal quantity of blood is estimated to be one-twelfth to one-fourteenth of the body weight, and clinically the rapid loss of one-half of this amount proves fatal.

Various “rules o’ thumb” have been offered, based on the blood-pressure readings and hematologic estimates, indicating when to transfuse and when it is safe to wait. Dorrance considers it imperative to transfuse when the count falls to 1,000,000 red blood-cells and 20 per cent hemoglobin, or below, and optional when the red cells are 1,500,000 and hemoglobin 25 per cent. Depage studied wounded soldiers and found that when the red cells fall below 4,500,000 in three hours, 4,000,000 in eight hours, or 3,500,000 in the first twelve hours, the patient will probably die unless transfused. Others have considered the blood-pressure readings as the most reliable indicator, pointing out that systolic pressure below 80 mm. Hg meant danger. Hicks relied solely on clinical symptoms, especially “the obstinate jactitations and resistance to comply without wishes in regard to treatment, coupled with the persistent indistinctness of pulse.” Robertson warns us against using ordinary resuscitative measures before resorting to transfusion. Our clinical observations bear out his belief that permanent degenerative changes occur in the organism when the exsanguinated condition persists for more than a few hours. We advise transfusion when in doubt. From experiments, Rous and Wilson demonstrated that the amount of hemoglobin retained in the severest hemorrhage is above the point necessary to sustain life. Unless the blood withdrawal is too rapid, the organism replaces this bulk by substituting plasma which the body retains in reserve, and thus maintains blood-pressure. In animals bled investigators were able to raise and maintain the blood-pressure reading by the injection of either horse serum or gum acacia (7 per cent). The effect



of normal saline solution was only transient, as this quickly leaves the vessels for tissues and urine. David and Curtis showed that dogs bled under similar conditions, until there was cessation of flow at the carotid, could be resuscitated either by injection of physiologic serum or by transfusion. However, in the eighteen hours following this experiment, 77 per cent of the dogs treated with serum died, and only 6 per cent of the animals transfused succumbed. In all but two cases in this series of acute hemorrhage the transfusion was life-saving or greatly beneficial. In the two unsuccessful cases, the patients were temporarily restored, but later died, due to the continuation of the bleeding.

The results of transfusion on the weak, starved, and anemic patient, as a supportive measure preliminary to operation, are eminently gratifying, as is evidenced both by the increased ability to withstand the operation and by the rapid postoperative convalescence. In the anemic cases in which the patients are to be submitted to abdominal operation transfusion is especially indicated. It may be safely asserted that in practically all operations in which the gastro-intestinal tract is opened there is more or less soiling of the peritoneum, which potentially spells peritonitis. It is the normal resistive elements of the organism which prevent this eventuality or limit it to a small area. In those cases in which the resistance of the body has been impaired by chronic bleeding, malignancy, and chronic infection, this complication is most frequently seen. The value, then, of transfusion as a preliminary measure is illimitable.

*Group 3. Bleeding.*—The general oozing which follows certain operations, especially in intensely jaundiced patients, has always been a source of grave concern to the operator, who, in most instances, has been without efficient means of checking it. The results of blood transfusion in these cases have been strikingly good; usually the hemorrhage ceases almost immediately, and the patient's improvement is quickly obvious. In certain cases, usually of the malignant type, in which the biliary obstruction has not been relieved by the operation, the hemostatic value of the transfusion rapidly decreases after forty-eight to seventy-two hours, and the patient may start bleeding again. Also, in the oozing occurring after operations on the stomach and intestines, transfusion alone will often be followed by complete and permanent cessation of bleeding and the rapid convalescence of the patient. The bleeding in ulcers of the stomach and duodenum is usually due to an erosion of one of the larger vessels, and transfusion should always be considered preliminary to, or in association with, a laparotomy for the excision of

the ulcer. For the postoperative bleeding in patients suffering from blood dyscrasia, transfusion is an effective hemostasis, but probably has no effect on the ultimate course of the disease. It is of interest that, clinically, the use of an anticoagulant in the transfused blood not only does not retard the coagulability of the recipient, but possesses an equal power of hemostasis with the undiluted blood administered by the syringe-cannula method. Experimentally, this observation was borne out in a series of 41 transfusions by the citrate method, in which the coagulation time of the recipient was tested by means of a Boggs' coagulometer and by Lee's test-tube method, just prior to, and immediately following, the transfusion. In 25 instances (58 per cent) the coagulation time was lowered from one to six minutes; in 6 (14 per cent) it was not affected, and in 12 (28 per cent) it was increased from one to three minutes. The coagulation time of a hemophiliac, not included in this series of tests, was taken before transfusion, and recorded as twenty-three minutes. Five minutes after the transfusion of 500 c.c. of citrated blood the coagulation time was three minutes; twelve hours later it was eight minutes; and on the fourth day after the transfusion the coagulation had returned to 20.

*Group 4. Acute toxic and septic conditions.*—The cases included in this group were for the most part infections following abdominal operation, and while the results are not encouraging, largely because of the fact that the patients were hopelessly ill before transfusion was employed, we believe that if given shortly after or, in some instances, before the operation, blood transfusion offers a reasonable means of combating infection.

*Group 5. Leukemias.*—As a temporary supportive measure for the correction of the anemia the results in the ten cases in this series justify the employment of transfusion.

*Group 6. Shock.*—In this series the diagnosis of surgical shock has been made in the cases of postoperative patients in whom there is no tenable etiologic factor for the production of the chain of symptoms usually attributed to this condition. The clinical diagnosis is often disproved on reopening the abdomen or at necropsy by the presence of "concealed" hemorrhage or fat embolism. In the one case in this series transfusion was without beneficial effect.

#### METHOD OF TRANSFUSION

Since December, 1915, we have employed the citrate method exclusively, and it has been used in this series of cases in 1001 instances.

and permitted to flow into the vein of the recipient. It is advisable to have the blood run in slowly in order to guard against suddenly overloading the right side of the heart, and in order to watch for any untoward effects on the patient. A marked slowing of the pulse, syncopal attacks, dyspnea, cyanosis, a sensation of cardiac oppression or excruciating pain throughout the body, especially localized in the small of the back, should be interpreted as danger-signals, and if these persist after temporary stopping of the flow, it is advisable to conclude the operation at once, and another donor should be secured.

The amount of blood to be transfused should be dependent on several factors, namely, the age of the patient, the presence of associated physical impairments, such as cardiac lesions, arteriosclerosis, etc., and the pathologic condition for which the transfusion is indicated. Unless for the purpose of replacing a large bulk of blood lost from an acute hemorrhage, the impression received from the study of this series of cases would indicate that better results are to be expected from the use of a relatively small quantity, 500 to 750 c.c., repeated in from five to seven days, rather than from a single transfusion of a larger amount. While the evidence is most conclusive that the transfused blood lives for a time at least as a transplant, yet a greater value in many of the anemic conditions lies in its stimulating effect on the blood-forming organs of the recipient, as is evidenced by the secondary rise in the hemoglobin and blood-picture, which occurs four or five days after the transfusion.

#### DONORS

In the selection of a suitable donor, a young, healthy, robust person is desired. Our results tend to corroborate the observations of Peterson, that the value of the transfusion is largely dependent on the individual donor. One donor's blood may exhibit remarkable powers of hemostasis; that of another may induce unusual hematopoietic stimulation, and that of another, owing to the presence of some antibody, may exert real antitoxic effect. The blood of every donor should be tested for syphilis and as to its compatibility in reference to agglutination and hemolysis. The seriousness of transmitting syphilis or other diseases, especially to those patients in whom there is no urgency for the transfusion, cannot be overestimated. As our ability for detecting syphilis by examination and Wassermann test is within limits, and as there is a possibility of the infection of the donor subsequent to his examination,

the chances of transferring syphilis, while admittedly small, should always be considered, and unless the transfusion is performed in emergency, this possibility should always be explained to the patient. Two instances of syphilis transmission are reported in the literature. In our series syphilis was transmitted by transfusion in one instance. This patient had been receiving a series of transfusions; the blood of the donor, in each instance, was Wassermann negative. One man who had served as a donor about twelve days prior to a skin eruption was suspected as the infecting donor, but this could not be proved.

Since July, 1916, the blood of the prospective donors has been tested according to the Moss agglutination test, as modified by Brem and Sanford. In instances of the new-born, when it is necessary to transfuse in order to check hemorrhage, Cherry and Langrock have shown, in a series of 34 tests, that the mother is always a suitable donor.

In an emergency such as that following an acute hemorrhage, when the life of the patient is dependent on an immediate transfusion, it is justifiable to use a donor without a preliminary test. In such instances the operator should allow the first 200 c.c. of blood to run in slowly. If the patient shows symptoms of hemolysis, the operation should be concluded or another donor secured. In this series we used donors without preliminary test in eight emergency transfusions, and in none of the patients was there any evidence of hemolysis. These results, we believe, were due to good fortune.

In 1913 Ottenberg and Kaliski explained that in the instance in which the serum of the donor is agglutinative to the cells of the patient, the plasma of the donor, on transfusion, will be diluted by the excess of the patient's plasma and will meet with a large excess of agglutinable cells. In practice they had four such transfusions with no unfavorable results. When it has been feasible we have always made it a point to use a donor in the same group as that of the recipient, but in a great number of instances, as in emergencies, and in cases in which a relative or volunteer donor is obtainable whose blood is not in the same group with that of the recipient, we have used donors whose cells are not agglutinable by the serum of the patient. In Group 4 there is a large percentage (43 per cent) of persons whose blood is suitable for transfusion with the blood of all the groups, and this point has been utilized in our emergency transfusions. Formerly, in cases of utmost urgency, we were forced to take a large chance by using an untested donor, but now there is always on call a list of prospective donors in Group 4 whose blood,

we have absolute confidence, will be suitable with that of any patient. In the entire series there have been no untoward effects on the donor from the loss of 500 to 750 c.c. On the other hand, the loss of blood in the majority of donors has been followed by a temporary gain in weight. Many of these donors continue their normal duties immediately on the conclusion of the transfusion. We have used especially robust persons as donors as often as eight times within twelve months.

There are three well-recognized accidents associated with and complicating blood transfusions, namely, acute dilatation of the heart, embolism from the introduction of air or clotted blood, and hemolysis. The first two accidents are absolutely preventable by the exercise of due caution as to the technic, the rapidity with which the blood is permitted to flow, and the limiting of the quantity of blood in cases of suspected cardiac and circulatory impairment. The third danger, due to the incompatibility of the blood of the donor and the blood of the recipient, is controllable by accurate blood tests. By the term "hemolysis" we mean the destruction of the red blood-cells with the liberation of the hemoglobin, and clinically we detect this by the finding of hemoglobinuria, increased urobilin in the urine, and phagocytosis. The gravity of the danger depends upon the degree of destruction.

#### REACTIONS

In 219 transfusions (21 per cent) of the series there occurred from fifteen minutes to one hour later a slight reaction of chill and fever, a temperature of 100° to 105°, with or without malaise, headache, nausea and vomiting, and diarrhea, and followed, in a small percentage of cases, on the third day after the transfusion, by an eruption of herpes. In another 15 per cent of transfusions there occurred a rise of temperature to 100° or above, not associated with chill and nausea. These were, in every instance, of a transitory nature, the temperature returning to normal in from twelve to thirty-six hours, and in only two instances was it at all probable that the good of the transfusion was vitiated by this complication.

The nature of such reactions is unknown. Various theories have been suggested, for example: (1) The introduction of a foreign protein; (2) the introduction of a citrate solution; (3) incipient coagulative changes in the transfused blood; (4) slight degree of hemolytic changes occurring after transfusion not sufficient to be evidenced by clinical test, and (5) incompatibility of the white corpuscles of the donor and recipient. All

may be factors, but in this series there was a striking relationship between the pathologic condition for which the transfusion was indicated, and the current of these milder reactions. A decidedly higher disproportion in the percentage was seen in those cases, such as pernicious anemia and advanced malignancy, in which there were active hemolytic changes. In some of these the intravenous introduction of normal saline alone was followed by similar reactions.

In 12 instances there were group reactions. The blood of three of these patients had been tested by the old macroscopic test, and the others by the method of Brem and Sanford. In every case in which the blood had been grouped by the microscopic test we were able later to locate an error in the testing. Most of these were due to a clerical error in recording the group of the donor or the recipient. In one patient, supposedly in Group 2, attempts were made on two different occasions to inject blood from a donor in Group 2, and both times we were forced to stop because of the occurrence on the table of a severe reaction. Later this patient's record was reviewed, and he was found to be in Group 3 instead of Group 2. Retesting proved this, and subsequent transfusions with Group 3 donors were unattended by any reaction. These reactions are most typical. They occur early after the introduction of 50 or 100 c.c. of blood; the patient first complaining of tingling pains shooting over the body, a fullness in the head, and an oppressive feeling about the precordium, and, later, an excruciating pain localized in the lumbar region. Slowly but perceptibly the face becomes suffused—a dark red to a cyanotic hue; respiration becomes somewhat labored, and the pulse-rate, at first slow, sometimes suddenly drops as many as 20 to 30 beats a minute. The patient may lose consciousness for a few minutes. In one-half of our cases an urticarial eruption, generalized over the body or limited to the face, appeared along with these symptoms. Later the pulse may become very rapid and thready; the skin becomes cold and clammy, and the patient's condition is indeed grave. In from fifteen minutes to an hour a chill occurs, followed by high fever, a temperature of 103° to 105°, in which the patient may become delirious. The macroscopic appearance of hemoglobinuria is almost constant. In three such instances the symptoms were not recognized at the time of the transfusion, and 500 c.c. of blood were injected. All the patients died, two in one and three hours respectively, following the transfusion, and one became comatose shortly afterward and died thirty hours later. In the other 9 instances the symptoms were early recognized and interpreted,

According to Howell, the rôle of calcium in the phenomenon of coagulation is to activate prothrombin into the formation of thrombin (the ferment), which in turn activates fibrinogen into fibrin. By the addition of citrate of soda coagulation is prevented by the chemical immobilization or stabilization of the calcium without forming precipitate. Extensive intravenous injection of citrate of soda deprives the blood and tissues of calcium, and the symptoms of convulsions, tonic and clonic, tetanic paralysis, and dyspnea, are the results of the decalcification of the nervous system. To combat this Hedon would administer calcium in the proportion of one atom to three molecules of the trisodic citrate. Lessahn, experimenting with a 10 per cent solution, found the toxic dose equivalent to 0.3 gm. per kilo, and later Carter showed that the more concentrated the dosage, the smaller the lethal dose. He found the lethal dose with a 2 per cent solution to be 0.835 to 1.24 gm. per kilo. Early in this series it was observed that there was a tendency for the milder reactions to occur in cycles, which corresponded in a striking manner with the preparation of fresh citrate solution. It was observed that citrate in solution rapidly deteriorates, and the importance of employing freshly prepared solution was thus emphasized. From the recognition of the fact that the coagulative properties of different bloods vary in different persons, as evidenced by the occasional coagulation of blood withdrawn from the donor in a 2 per cent citrate solution, we have substituted a 0.24 per cent citrate solution.

#### TECHNIC

The arm of the donor is prepared in the usual manner. A tourniquet is lightly applied above the elbow and the median basilic or the median cephalic vein is either punctured with a large-sized needle or exposed by a small incision, and a cannula introduced. By a simple, yet very ingenious little trick, advised by Watson, we have been aided greatly in introducing a large-sized Kaliski (gage 11) needle into the lumen of the vein. By means of a small, straight intestinal needle, inserted transversely, the vein is transfixed to the skin, the needle passing through its upper segment. With the end of this transfixing needle as a handle, the vein is steadied, and the cannula needle, directed parallel with the line of the vein, can be readily pushed beneath the level of the transfixing needle into the lumen of the vein (Fig. 217). The blood is received in a sterile graduated glass jar containing 30 c.c. of a 2 per cent sterile solution of sodium citrate at the bottom. While the blood is running, it is

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## REACTION FOLLOWING BLOOD TRANSFUSION THE SODIUM CITRATE METHOD\*

V. C. HUNT

In all the blood transfusions done at the Mayo Clinic in the past two and one-half years the sodium citrate method, advocated by Lewisohn,<sup>3</sup> has been used. The sodium citrate is chemically pure and sterilized in one of two ways—by boiling or dry heat. When sterilized by boiling, distilled water, previously boiled for ten minutes, is used; the citrate is then added, and the boiling allowed to continue for ten minutes longer. Sterilization by dry heat is carried out by putting 10 grains of chemically pure sodium citrate in papers and placing in a sterilizer for thirty minutes at a temperature of 248° F. By either method an approximately 2 per cent solution is made by adding 9 grains of sodium citrate to the ounce of distilled water, and the solution is used in the proportion of 30 c.c. of 2 per cent sodium citrate filled up to 250 c.c. with blood for whatever amount of blood is to be transfused, making approximately a 0.2 per cent citrated blood, as it is given to the recipient.

The apparatus consist of one or two 500 c.c. graduated flasks, depending on the amount to be transfused, a glass salvarsan tube drawn out at its lower end for tube connection and graduated to 300 c.c., a piece of rubber tubing one-fourth inch in diameter and four feet in length, several ten-inch pieces of tubing of the same diameter, a few Lewisohn-Kaliski 15-gage needles, a glass stirring rod, and a tourniquet. The glassware and tubing are sterilized by boiling in distilled water, and the needles by carbolicizing.

The median basilic vein in both recipient and donor is the one of choice; however, where repeated transfusions are done or where these veins are small, it is at times necessary to resort to the external jugular vein or the veins of the leg. The arms of both the recipient and donor are surgically prepared.

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In taking the blood from the donor a 10-inch piece of rubber tubing is connected to a Lewisohn needle and 2 per cent sodium citrate is allowed to pass through it. After the tourniquet has been lightly applied to the donor's arm, the vein is transfixed through its upper segment after the method of Watson, the Lewisohn needle is inserted into the vein against the blood-stream, and the blood is allowed to run into the flask containing the sodium citrate, which is added in the proportion of 30 c.c. filled up to 250 c.c. with blood. As the blood comes from the donor it is stirred with a glass rod in order to mix it thoroughly with the sodium citrate, and it is essential that the blood should run a steady stream from the donor in order to avoid the coagulation of droplets.

After the necessary amount of blood has been taken from the donor, a tourniquet is lightly applied to the recipient's arm, the prominent vein at the elbow is transfixed, and the Lewisohn needle inserted with the blood-stream. When the needle has fully entered the lumen of the vein the tourniquet is removed, and from the salvarsan tube connected to the needle by long tubing a small amount of warm normal saline is allowed to enter the vein before the blood is added and given by the gravity method. It has been the custom to give 500 c.c. of citrated blood at a first transfusion and 750 c.c. for subsequent transfusions when they were repeated.

The Brem method for determining groups in the patients and in the selection of donors has been used at the clinic for the past two years, and is briefly reviewed herein. Iso-agglutination was discovered independently by Landsteiner and by Shattock in 1900. Landsteiner suggested that the groupings could be explained by assuming the existence of two agglutinins, of which the second group possessed one, the third group the other, the fourth group both, and the first group neither, in each case the cells being susceptible only to that agglutinin which does not exist in the individual's own serum. The groups are as follows:

*Group 1.*—The serum of Group 1 does not agglutinate corpuscles. The corpuscles are agglutinated by the serum of Groups 2, 3, and 4.

*Group 2.*—The serum of Group 2 agglutinates the corpuscles of Groups 1 and 3. The corpuscles are agglutinated by the serum of Groups 3 and 4.

*Group 3.*—The serum of Group 3 agglutinates the corpuscles of Groups 1 and 2. The corpuscles are agglutinated by the serum of Groups 2 and 4.

*Group 4.*—The serum of Group 4 agglutinates the corpuscles of

Groups 1, 2, and 3. The corpuscles are not agglutinated by serum.

Ten per cent of all persons are in Group 1, 40 per cent are in Group 2, 7 per cent are in Group 3, and 43 per cent are in Group 4. Groups 1 and 4 have been called universal groups because of the fact that a Group 1 recipient may be safely transfused, and with benefit, by any donor, and a Group 4 donor is a safe and beneficial one to use for any recipient. The transfusions of patients in the Mayo Clinic have been done in their own groups, except in the Group 1 recipients, who have not always been transfused with blood of their own groups, and Group 4 donors have been used many times for recipients of other groups or those whose groups were not known, as was the case in a number of emergency transfusions.

During the past two and one-half years the sodium citrate method of transfusion has been used in approximately 1400 transfusions. However, this analysis of transfusion reactions is based on the review of 726 transfusions performed during 1917. The total number of patients transfused was 301, of which 123 were cases of pernicious anemia and the remaining 178 were in secondary anemias from various causes, and blood diseases in which transfusion seemed to be indicated. The conditions consisted chiefly of uterine fibroids, malignant disease, secondary anemia of unknown origin, common duct obstruction with prolonged coagulation time, bleeding duodenal and gastric ulcers, ruptured tubal pregnancy; uterine hemorrhage, gunshot, splenic anemia, leukemia, hemophilia, purpura, hemolytic jaundice, endocarditis, colitis, miliary tuberculosis, actinomycosis, septicemia, etc. One hundred thirty-one of the number were surgical cases. In 74 cases one or more preoperative transfusions were done to decrease the operative risk, as in severe grade secondary anemia, and prolonged coagulation time in obstructive jaundice. In 75 transfusions were done postoperatively for hemorrhage or poor general condition. The indications for blood transfusion in this series of 726 transfusions were:

1. To replace blood lost, as in the acute hemorrhages.
2. To stimulate the hematopoietic organs, as in the cases of pernicious anemia and secondary anemia of long standing.
3. To add a thromboplastic substance in those cases with prolonged coagulation time.

In the entire number of transfusions for the year, post-transfusion records were accessible in all but 26, making 700 such records for analysis. In 7 of these the wrong donor was used and reaction occurred on

the table, because of agglutination of the donor's corpuscles. Since severe reaction occurs in 100 per cent of cases in which agglutination of the donor's corpuscles takes place, it seems advisable not to include these 7 cases for the analysis of post-transfusion reaction, which leaves 693 transfusions in which the grouping was correct.

Frank post-transfusion reaction is characterized by chill and fever, nausea and vomiting, and frequently urticaria and severe headache. In the entire series such reaction occurred in 130 cases (18.7 per cent); in 10 others there was fever but no chill, and these, it seems, should be included as true reactions, making 20.2 the total percentage of reactions.

On dividing the cases into pernicious anemia, of which there were 123 in whom 403 transfusions were done with post-transfusion record, and the anemias, other than pernicious anemia, and other conditions for which transfusion was performed, of which there were 178 patients who received 294 transfusions with post-transfusion records, it is seen that a frank reaction occurred 94 times (23.3 per cent) in pernicious anemia. In the conditions other than pernicious anemia, reaction occurred 43 times (14.8 per cent), a difference of 8.5 per cent between the two groups.

The foregoing symptoms of reaction in these cases were manifested usually within an hour after the transfusion; however, in a very small number it was delayed for from twelve to twenty-four hours. In none was there any evidence of hemolysis and there was no hemoglobinuria. The severity of the chill was quite variable, at times lasting but a few minutes, but usually fifteen to twenty minutes and occasionally a half-hour. The degree of fever following the chill varied between 100.6° to 105°, being higher the more severe and lasting the chill. It was usually of but a few hours' duration, and only exceptionally lasted more than twelve hours. In some of the cases in which there was no chill or rise of temperature there were subjective symptoms, such as nausea and vomiting, headache, and, occasionally, urticaria and the skin manifestations of serum reaction, which were quite transient.

In the whole series of 726 transfusions there were seven instances, approximately 1 per cent, in which, through some error in the grouping, a wrong donor was used; that is, one whose corpuscles, as was shown by subsequent grouping, were agglutinated by the recipient's serum. In each of these severe reaction occurred on the table, and in all instances when less than 150 c.c. of the citrated blood had entered the recipient's circulation. The manifestations of reaction in these cases were entirely

different from the post-transfusion reactions. They occurred very suddenly, the first symptom being pain in the chest, usually in the precordial area, marked dyspnea, and severe pain in the back, in the lumbar region. Cyanosis, edema of the face and eyelids, flushing of the skin of the entire body, and often urticarial spots were seen. The pulse-rate suddenly dropped very appreciably. In a few instances there has been temporary loss of consciousness with transient muscular contractions. In all the cases there was nausea and at times vomiting. All these patients had very severe chills soon after the transfusion, with fever, sometimes as high as  $105^{\circ}$ . There was hemoglobinuria. In 5 of the cases the transfusion was discontinued when the above symptoms appeared, and each one received no more than 180 c.c. of citrated blood; all recovered after a more or less stormy convalescence. In the other 2 cases the symptoms were not interpreted to be those owing to the agglutination of the donor's corpuscles and the transfusion was continued up to 500 c.c. One of the patients became comatose and died thirty hours later, and the other died two hours later. Since such symptoms are so constantly manifested when agglutination of the donor's corpuscles takes place, with the introduction of less than 150 c.c. of citrated blood, the transfusion should be stopped immediately and further grouping studies made of the blood of both donor and recipient. In all probability the fatalities occurring after transfusion are due to the agglutination of the donor's corpuscles. Ottenberg, in a fatal case, in which agglutination of the donor's corpuscles occurred, found in the smears many polymorphonuclear leukocytes containing red blood-cells. He thinks that there is a close relationship between agglutination and phagocytosis, and concludes that agglutinable blood is useless, as the cells are foreign and do not remain in the circulation.

The cause of post-transfusion reactions by the sodium citrate method has as yet not been established. Several factors lend themselves as possible etiology, chief of which are: (1) The preparation of the sodium citrate solution; (2) incompatibility in the white cellular element and blood-platelets, and (3) difference in proteins of the blood.

Lewisohn,<sup>4</sup> in his work, found that as much as 5 grams of sodium citrate can be given intravenously to an adult with safety, but that larger amounts are extremely toxic. Using a 2 per cent sodium citrate solution in the proportion of 30 c.c. filled up to 250 c.c. with blood, and making an approximately 0.2 per cent citrated blood, 1000 c.c. of which contains but 2 grams of sodium citrate, excludes the possibility of tox-

icity as a cause for the reactions. By using a chemically pure drug the possibility of existing impurities as a cause is readily disposed of; however, it has been seen that a lower percentage of reactions attends the transfusions when the citrate solution is prepared fresh for each transfusion. Because of the fact that chemically pure citrate solution was prepared in a similar way for each transfusion, and that in but 20.2 per cent of all the transfusions did reaction occur, it seems justifiable to exclude the drug as a possible cause for reaction.

By grouping the blood according to the powers of agglutination the possibility of hemolysis is excluded, but no conclusive work on the compatibility of the white cells and blood platelets, nor the possibility of existing differences of proteins has as yet been reported, which leaves these two factors open as causes for post-transfusion reactions. The amount of blood transfused seems to bear little relationship to the percentage of frank reactions. While we have had few cases in which less than 500 c.c. of citrated blood has been transfused, there seems to be no difference in the percentage of reaction whether 500 or 750 c.c. is used.

The patient's general condition seems to be an important factor in the percentage of post-transfusion reactions. The patients with pernicious anemia were, as a group, in much poorer condition than those in the group in which transfusion was done for conditions other than pernicious anemia, they having an 8.5 per cent higher incidence of reaction, which would seem to indicate that patients in poor condition are more susceptible to reaction after transfusion. This is given further support by the decreased incidence attending subsequent transfusions, since only 40 per cent of the patients with pernicious anemia, having reactions after the first transfusion, had reactions after subsequent transfusions; 27 per cent had reactions with the second transfusion, 22 per cent with the third, 12 per cent with the fourth, and 7.5 per cent with the fifth.

Our experience has not led us to believe that some donors are more capable than others of producing reaction. It has been stated by advocates of the whole blood methods of transfusion that the sodium citrate method is attended by a higher percentage of reactions than the whole blood methods. It is a well-known fact that any intravenous introduction of a quantity of a foreign solution is followed by a certain percentage of reaction characterized by chills and fever, as in normal saline, salvarsan, etc. Some reports of exceedingly low percentages of



reaction, following the whole blood methods of transfusion, have appeared in the literature. Unger's report, in whose cases reaction occurred in 15, or 9 per cent of 165 transfusions, is a striking example; there are others in which there is a much higher incidence. Meleney, Stearns, Fortune, and Ferry reviewed 280 transfusions done by various methods, with occurrence of reaction in 64.8 per cent by the sodium citrate method, and 64.4 per cent by the syringe cannula method, from which they concluded that the method of transfusion had nothing to do with the production of reaction.

In about 60 per cent of the transfusions for pernicious anemia in our cases in which reaction occurred marked improvement in the blood picture took place after the transfusion in spite of the reaction. The remaining 40 per cent showed the poor response which is seen at times in the absence of reaction.

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## **SKIN AND SYPHILIS**



# CLINICAL STUDIES IN CUTANEOUS ASPECTS OF TUBERCULOSIS

## I. "TUBERCULOUS" PURPURA, ERYTHEMA MULTIFORME, AND ERYTHEMA NODOSUM\*

J. H. STOKES

The tendency of recent advances in the study of the etiology of dermatoses has been increasingly to show that many supposed clinical entities, so styled on purely morphologic grounds, have a multiple etiology. One of the conditions undergoing such etiologic revision is the erythema group, including the clinical entities of erythema multiforme and erythema nodosum. The work of revising our outlook on erythema multiforme, purpura, and urticaria was well begun by Osler in 1895. Erythema nodosum is of particular interest because on its border lie erythema induratum and the group of dermatoses designated after Darier as "tuberculids," whose intimate relation to tuberculosis is now generally accepted. Erythema nodosum, on the basis of the experimental evidence cited herein, is in a fair way to be at least partially allied to this group, and it awaits only a sufficient body of clinical evidence and some corroborative work to establish its connection. The fact that the majority of American dermatologic tests have not yet given this phase of the matter the attention it deserves probably accounts for the seeming unfamiliarity of internists, surgeons, and general diagnosticians with the very great diagnostic and prognostic significance of purpura, erythema multiforme, erythema nodosum, and the tuberculids. My own interest in the relation of this group of dermatoses to tuberculosis was aroused by the death of a patient having the miliary type of the disease, following an onset in the form of purpura rheumatica and succeeded by erythema multiforme.

The material here presented forms part of a series of approximately 40 cases of erythema nodosum, erythema multiforme with purpura, erythema induratum, and the various types of papulonecrotic tuber-

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CASE 2 (A-49238).—A male, aged thirty-four, has been under observation in the clinic for seven years. In 1911 he was referred for treatment by his home physician because of shifting pains, stiffness, and purpura of ten days' duration. While the patient's physician considered that the purpura suggested rheumatism, personally he was inclined to suspect tuberculosis, of which, in miliary form, the patient's sister had died. Six months before the onset of symptoms the patient had been in bed with "typhoid" for twelve days. At the time of examination purpuric lesions were present on the shins, shoulders, and chest. An increase in temperature was reported; he had lost appetite, but no weight. Evanescent râles were heard posteriorly over the left lung. Enlarged glands in the left axilla and cervical regions were noted, and the roentgenogram showed beginning tuberculosis of both apices; the sputum, however, was negative. In 1914 the patient was again seen for a brief period, but the tuberculous process was then quiescent. In 1918, seven years after the onset of the purpura and three years after the patient's last illness was last observed, my assistant was called to see him during an attack of erythema nodosum, which I had the opportunity to observe as it was subsiding. At this time numerous deep subcutaneous erythematous nodes over the tibiae, and many less erythematous, smaller, and patchy shotty indurations were found. The chain of lymphatics along the left pectoralis major and the axillary and mammary nodes were enlarged, and, in some instances, caseous and calcified. Subsequent resection of these glands at operation established the pathologic diagnosis of tuberculosis.

This case differed from the conventional picture of erythema nodosum only in the greater pallor and smaller size of many of the nodules, in the absence of the ecchymotic color changes, and in the generally lesser activity of the process. At its height, however, it was quite within the usual limits of variation of the clinical picture of erythema nodosum. The purpura, with rheumatoid pains in the early years of the disease observed in this patient, is one of the features common to other cases to be cited hereinafter.

The following case is illustrative of the manner in which a purpuric onset and a tuberculid may precede, by months or years, the gross clinical evidence of active tuberculosis.

CASE 3 (A-154673).—A man, aged thirty-one years, a tailor, first came to the clinic in 1916 because of a scrotal hernia, which was operated on with good results. At that time the patient gave a history the significance of which was not appreciated until later. A year before his first examination he had an attack of grip, followed by a purpuric eruption. The macules were from a pinhead to a dime in size; some of

them had "blistered" and left scars on the extremities. Apart from a small colloid goiter, a hernia, and a lichenified scrotum, his examination was negative. No radiographic examination was considered necessary, in view of the absence of symptoms. One year and a half after this examination and the operation for hernia, the patient returned giving a history of "sciatica" and of an abscess that had drained through the buttock and had left a persistent sinus. Bismuth injection demonstrated a draining sacro-iliac abscess. The patient was then seen by a dermatologic consultant because of the scars on the legs, which were typically those of a tuberculid, although there were then no active lesions. The operation on the sinus disclosed a tuberculous process, probably originating in the lumbar or sacral spine.

If a dermatologist had seen the purpura and the tuberculid at the first examination, two years previously, and appreciated its significance, a more thorough search might have disclosed the focus.

CASE 4 (A-157847).—A woman, aged thirty-three years, a clerical worker, came to the clinic in 1916 with a history of severe anemia two years before, from which she had recovered under treatment with iron. A year later a lump, not, however, preceded by any sore throat, appeared on the right side of the neck. In fact, the patient had never had sore throat or tonsillitis. Abruptly, two months after coming to the clinic, and nearly two years after the appearance of the glands, the legs swelled markedly without apparent cause, and were covered with raised red lumps. The patient had a temperature of 103° and was confined to bed for two weeks; the temperature subsided, but the edema persisted. Examination disclosed a pale, rather fat girl, with numerous erythematous nodules and hyperemic plaques on both legs and arms. The plaques in particular were more suggestive of erythema multiforme than of the conventional erythema nodosum. Their comparative pallor may have been due to the anemia. None of the lesions had shown any tendency to ulceration. The temperature was normal; hemoglobin, 40 per cent; a marked glandular enlargement on the right side of the neck was shown, by subsequent excision for diagnosis, to be tuberculous. The x-ray of the chest showed healed pulmonary tuberculosis involving both apices. The tonsils were markedly septic. After the removal of the tuberculous glands a tonsillectomy was performed. This, however, did not prevent the continued appearance of nodular lesions on the legs. Although these did not at any time become ulcerative, the picture approached more and more nearly that of erythema induratum of Bazin, for which we treated the patient a year later.

The typical onset of erythema nodosum in this case, two years after the appearance of the glands, was combined with the appearance of

lesions suggestive of erythema multiforme. The nodose lesions persisted and recurred, constituting a chronic erythema nodosum. To speak, even after tonsillectomy had removed a possible atrium of infection for diphtheroid and other organisms, and a block dissection had removed a portion of the tuberculous focus. There was nothing to suggest a dental source of infection. That the tuberculous focus, which was the probable source and perpetuator of the process, had not been done away with is shown by the subsequent reoperation for recurrence in the glands. The following is a case of somewhat similar type:

CASE 5 (A-22802).—A girl, aged twenty-three years, a rancher three years before coming to the clinic had sustained surgical removal of cervical glands and tonsillectomy, at which time a pathologic diagnosis of tuberculous adenitis was made. The tuberculous process had extended to new glands in spite of tuberculin and an outdoor regime. For two weeks before her examination in the clinic she had felt tired and her legs had ached, following which an eruption of "lumps" appeared abruptly below the knees, on the posterior surface of the legs. These were beginning to involute spontaneously. On examination, blue, moderately infiltrated plaques were recognized on the calves of the legs; these disappeared under appropriate treatment. The radiograph of the chest was negative. The tuberculous nature of the adenitis had been established by the previous pathologic examination, and there was a visible and palpable recurrence.

The onset in this case suggests a mild erythema nodosum. In its distribution on the calves and in the relative indolence of the lesions it approached more nearly the type of erythema induratum, and should be compared with the preceding case and the last case in the series. The whole picture developed three years after the removal of a tonsillar focus, but while the tuberculous focus was still active. The next case, while perforce left indeterminate, illustrates very well the type of erythema nodosum onset which may eventuate in an active tuberculous focus, such as that suspected in Case 1 and identified in Case 2.

CASE 6 (A-188556).—A man, aged forty-three years, reported at the clinic with the statement that three weeks before he had caught a common cold. He felt weak since the onset of the infection, and had had a cough and expectoration for two weeks. There were some aching and edema of the legs. The past respiratory history was not significant. On examination a very marked right cervical adenopathy was found. The patient's afternoon temperature was 100°. The extensor surfaces of the arms and legs were studded with deep-seated nodules, varying

from 0.5 to 1.5 cm. in diameter, and from a yellowish pink to a deep violaceous color. Over the anterior tibial region there were numerous larger lesions, which were, on the whole, however, somewhat smaller and less ecchymotic than those of a well-developed erythema nodosum, and showed signs of early involution. The lesions about the wrists were of the erythema multiforme type, and few in number. A few papulopustules had appeared. Examination of the thorax disclosed prolonged breath-sounds and increased fremitus over the right apex. The x-ray examination of the chest, a Wassermann test, and the blood culture were all negative.

This case is especially instructive because, in addition to presumptive signs of tuberculosis in the form of localized lymphadenitis, the cutaneous manifestations included erythema multiforme lesions about the wrists, erythema nodosum over the tibiae, and a few pustular lesions suggesting the acute generalized miliary tuberculosis of the skin seen in children and more rarely in adults. The lung signs were inconclusive but suggestive.

The next case illustrates how the appearance of an erythema multiforme as a manifestation of obscure tuberculosis may be followed by the development of a tuberculid. The history aligns itself with that of the patient of Case 3, who gave a history of a purpura followed by a papulonecrotic tuberculid, as an illustration of the importance of the individual history of cutaneous manifestations in a proper interpretation of the relation of purpura and erythema multiforme to tuberculosis.

CASE 7 (A-224920).—A young girl, aged sixteen years, gave an extraordinary family history, on the mother's side, of tuberculosis in both direct and collateral lines. The mother herself had been examined in the clinic, although not by a dermatologist, and the presence of "yellowish-brown, stain-like spots" on the legs had been noted. A diagnosis of anemia and septic teeth was made in the mother's case; the daughter was referred to us on a provisional diagnosis of Raynaud's disease because of the cyanosis of her hands and the history of attacks of "blisters" on the fingers. Her father described to us a fairly typical though abortive attack of erythema multiforme involving her hands and wrists which had preceded the present trouble by about four years. The description of the condition at the time of the examination was that of a vernal attack of folliclis, of which the scars were distinctly visible on the dorsal aspects of the terminal phalanges. Similar lesions had developed on the toes. The general examination disclosed the presence of râles and increased dullness over the right lung apex, although the examiner was not in the least under the influence of a preconceived notion about the case, since he had made a diagnosis of Raynaud's dis-



ease. Although the radiogram of the chest was negative, we advised in view of the history and the tuberculid scars, that an antitubercular regimen be adopted. The tonsils had been removed for recurrent tonsillitis four years before the onset of the folliculitis.

The last case of the series illustrates the association of purpura with a typical tuberculid, erythema induratum, and the prominent arthritic symptoms which might well lead to misinterpretation of the process in its earlier stages as a septic or rheumatic infection.

CASE 8 (A-233765).—A very large, florid woman, aged thirty years, decidedly overweight, whose father had died of empyema and lung trouble, was referred to my service for a very typical erythema induratum with papulonecrotic lesions and ulceration involving the centers of both legs. On examination it was found that the patient had many cutaneous nodes scattered over both extremities, with purpuric lesions over the arms, trunk, and chest. She had an arthralgia and myalgia of the right shoulder which prevented her from raising her arm to her head, and reported that six years before she had had "rheumatic fever." The tuberculid antedated the "rheumatism" by eight years. The tests were negative; tonsils only slightly septic; radiogram of the chest negative, and no glands were identified. The tuberculid responded rapidly to treatment, but the nodules in the upper extremities continued to recur.

This case represents a type of patient not unfamiliar to both dermatologist and internist, in which a florid and rather obese exterior conceals a focus of tuberculosis which at times cannot be identified. The case is included with the series to illustrate the association of purpura with a cutaneous lesion whose tuberculous character is now generally conceded.

Before summarizing the lessons to be drawn from such a series of cases, I shall further illustrate the diagnostic problems presented by erythema nodosum from the standpoint of tuberculosis by two examples drawn from clinically typical erythema nodosum, diagnosed as such in my records, but with the reservation that observation of their cases shall be continued for some time.

CASE 9 (A-194220).—A woman, aged thirty-two years, indoor worker after being "under the weather" for some time, presented herself looking decidedly ill. She complained of a slight sore throat, arthritis of the knees and ankles, and of having numerous large, deeply infiltrated nodose lesions of a dark reddish to purplish color in the pretibial region and on the front of the thighs. Typical lesions of erythema multiforme were found on the backs of the hands and on the neck. There was

nothing in the history to lead one to suspect tuberculosis. The tonsils were markedly septic, and several alveolar abscesses were demonstrated by the x-ray. The patient showed, however, physical signs of a slight right-sided pleurisy at the base and the radiogram was suspicious. The erythema nodosum disappeared entirely on salicylates, after which the pyogenic foci were removed; the patient improved rapidly, all pulmonary signs disappearing to such an extent that a contemplated sanitarium régime was given up.

There are no signs of a tuberculous process in this case four months after the attack of erythema nodosum, but an experience with erythema nodosum of the type illustrated by the foregoing cases would lead one to insist on further observation. Petroff, it will be recalled, has directed attention to the effect of intercurrent infection in temporarily lighting up tuberculous foci to the point at which they can be recognized for a brief time, only to disappear again with the subsidence of the incidental infection. Abt, in 1907, also suggested that it was the function of erythema nodosum to prepare the way for tuberculosis, a conception which loses none of its plausibility in this type of case by the further belief that there may be a true tuberculous erythema nodosum represented by the first eight cases of this series as well.

CASE 10 (A-235299).—A housewife, aged twenty-seven years, presented the lesions of erythema nodosum over the front of the thighs and pretibial region, many of them large and tumid, with marked arthritic onset. The patient had lost 15 pounds in weight during eight weeks of the acute process before she was first seen. She exhibited a definite hyperpigmentation overlying a pasty pallor. A history of tonsillitis some years before was obtained. The lesions were not and had not been painful, although in all other particulars they conformed to the strict erythema nodosum type, even to the ecchymotic changes. The tonsils were not septic, and the radiogram of the teeth was negative. The patient had a unilateral phlyctenular conjunctivitis, not especially suggestive of tuberculosis. On the other hand, the radiogram of the thorax showed a markedly thickened right hilus, indicating enlarged glands.

Although the patient made an almost miraculous recovery under salicylates, it would be folly to release her from further observation for the settlement of the question of concealed tuberculosis. Had her symptoms been accepted at their face value, no investigation of this question would have been made, and the condition would have been regarded as "rheumatic."

## DISCUSSION AND SUMMARY

The series here presented is too small for a satisfactory statistical summary, and for that reason will be incorporated for interpretation in another paper with the group of tuberculids of which it forms a part. Briefly, however, it is of interest to note that the clinical picture of tuberculous purpura, tuberculous erythema multiforme, and tuberculous erythema nodosum is made up of objective rather than subjective symptoms. Estimated by a rigorous standard, four of the first eight cases were positively demonstrated as tuberculous, and the remaining four were of a highly suspicious nature if not absolutely definite; two additional cases of erythema nodosum, morphologically conforming to the conventional or rheumatic type, were also suspected of being tuberculosis and are under observation. Of the eight original cases, the tuberculous focus in four was identified by pathologic examination; two were positive and one indeterminate in the radiogram of the chest; four showed physical signs in the lung and one was indeterminate, and four had visible and palpable adenopathy. No evidence of syphilis could be identified in any of the ten cases. Two of the patients had tuberculids of the papulonecrotic and erythema induratum type, and one of them had folliclis, a tuberculid of the fingers. Three presented purpuric lesions, three had lesions of the erythema multiforme type, and six had nodular lesions of the type met with in erythema nodosum, though of varying grades of acuteness and severity. In two of the cases of nodular erythema the onset was that of erythema nodosum and the localization approached that of erythema induratum. In one of these cases the nodose lesions were associated with a typical erythema induratum with ulceration.

Of the eight cases in the original group, three presented a family history of tuberculosis, and in one it was strongly suspected, though not absolutely definite. That the onset of the cutaneous manifestations is not necessarily coincident with the onset of the tuberculous infection is apparent from the fact that the shortest probable duration of the active process varied in the cases reported from five months to eight years. The usual points of inquiry in a history of tuberculosis, as to night-sweats, hemoptysis, etc., yielded little information. Only two patients had cough, none had night-sweats, and none showed blood in the sputum. The sputum of the two who coughed was negative. On

the other hand, five of the seven of whom data were available showed increased temperatures during the active process, varying from 99° to 103°. Only one presented a significant anemia (40 per cent hemoglobin). The absence of leukocytosis or the presence of a slight leukopenia, even in the febrile cases, was notable and in keeping with the suspected tuberculous etiology. The counts varied from 5000 to 9600.

The habitus and general condition of the patients afforded little clue to the nature of the disturbance, since the septic cases were indistinguishable from the tuberculous. Loss of weight does not seem to have been a conspicuous feature, although three out of the ten cases discussed showed sharp drops—from 8 to 21 pounds in from five to eight weeks.

The consideration of the possibility of a septic focus in these cases was of interest. In one of the patients the tonsils did not seem involved; in two they were mildly septic, but not markedly affected; a fourth with markedly infected tonsils had them removed without appreciable effect on the process, and two developed their first attacks—one of erythema nodosum and the other of folliculitis three and four years after the removal of the tonsils. While gross examination for an alveolar or gingival focus was negative throughout the series of ten cases, in one suspected case the patient had an alveolar abscess demonstrable by the x-ray; two cases were negative. Radiograms of the teeth were not taken in the remainder. The secondary focus of pyogenic or diphtheroid infection seems to be a negligible quantity in this group, although its importance is much more apparent in a review of the entire series of tuberculids. Four in ten had symptoms of a rheumatic character, in the form of myalgia, arthralgia, and neuritis. The modes of onset in the ten cases were slight—sore throat in two, cold and grip in two, typhoid, so called, in one, and by indefinite, non-localizing symptoms or the typical abrupt onset of erythema nodosum in five. The part played by the respiratory atrium is much more apparent in the larger series.

Dermatologically the differentiation of tuberculous from streptococcal or diphtheroid erythema nodosum can scarcely be worked out on so small a group of cases. A tentative personal view of the matter is as follows: While the two conditions are at times indistinguishable from each other on the score of acuteness, localization, and course, and this fact cannot be too forcibly emphasized, Table 1 embodies the main points of difference as the writer has seen them:

TABLE 1

**STREPTOCOCCAL ERYTHEMA NODOSUM**

Nodes larger, more edematous and brawny, more tense, and hemorrhagic. May reach the size of a small palm.

Greater involvement of the superficial tissues.

Distribution more apt to be over the front of the lower extremities, especially below the knees and over the front of the thigh; also around the larger joints.

Color changes more marked than in the tuberculous type. The brown element especially marked. Behaves typically like a bruise.

Symptoms in general more severe; progress more rapid, whole process more acute; tendency to self-limited course.

**TUBERCULOUS ERYTHEMA NODOSUM**

Nodes smaller; less marked peripheral reaction; hemorrhagic changes less marked. In their place may be purplish lividity, but usually only a well-developed erythema.

Nodules more circumscribed and deeper.

May appear on either front or back of the leg, but tends to localize posteriorly. May appear in smaller numbers or in crops or groups, or one or two on the upper extremities. May appear on the feet.

The nodule is paler at the onset, and progresses from pink to a livid purple or bluish tinge. If it persists, as erythema induratum, it remains bluish, softens, and may show a bullous surface or undergo necrotic sloughing. The nodules may present only a mild erythema, which subsides, leaving no color changes or only a faint yellow stain, or there may be colorless ones among the erythematous nodes, suggesting Wende's nodular tuberculosis of the hypoderm.

Process more indolent; lesions less tender or even painless; more persistent; may last months or longer, especially if there is little inflammatory reaction. Of material assistance in diagnosis is the concomitant occurrence of an indubitable tuberculid, such as folliculitis, or the papulonecrotic types of lesions or their scars.

Our experience with the diagnostic problems involved in erythema nodosum has led us to formulate for ourselves a series of procedures which should be carried out in all cases in order to establish or eliminate the possibility of a tuberculous infection. First of all a painstaking search of family and past history for evidence of tuberculosis should be made, even though the case seems typically of the rheumatoid type. In the same way the histories of patients suspected of having tuberculosis might well be canvassed for evidences of purpura, erythema multiforme, and erythema nodosum. In my experience with the larger group of tuberculids I have been impressed many times with the fact that a rheumatoid onset in this group of dermatoses should suggest tuberculosis almost as promptly as it does a focus of streptococcal infection. Arthritic and myalgic symptoms seem to have little differential value in eliminating tuberculous infection in these cases. Since the evidences of associated tuberculous infection in this group of conditions are largely objective, painstaking examination of the chest for physical signs and by radiograms should be made in every case. The throat and accessory sinuses should be examined for a collateral focus of pyogenic

infection, and a radiogram of the teeth should also be a part of the routine examination. Systematic observation of the temperature should be undertaken, with a leukocyte count. A careful search for enlarged glands should be made and repeated. I believe that cases of erythema nodosum are of sufficiently grave prognostic significance to warrant a period of observation and reëxamination, prolonged in proportion to the suspicions developed by the study of the case. Finally, I venture to suggest the aid which dermatologic consultation can render in such cases. One is surprised to see the readiness with which competent and even highly trained internists dismiss a purpura as "rheumatic," failing entirely to notice the tuberculid, or its scars, which lies beside it, or speculate on the probability of Hodgkin's disease in an adenitis when the evidence to prove it tuberculous is before their eyes in the form of a crop of papulonecrotic lesions. A certain amount of special experience and some special attention to this detail will add much to the diagnostic armamentarium of men in other fields who are called on to diagnose and deal with tuberculosis as a medical and surgical problem.

#### CONCLUSIONS

1. While it is impossible at the present time to dogmatize on the existence of a tuberculous type of purpura, erythema multiforme, or erythema nodosum, clinical and experimental evidence is collecting to show a close association between a tuberculous infection and cutaneous syndromes of the type mentioned. Whether the lesions themselves are due to the tubercle bacillus, and whether or not their appearance signals a flare-up in the tuberculous focus, cannot as yet be definitely stated. It is possible that a non-tuberculous infection which produces the erythema complex may uncover the tuberculous focus, so to speak, much as measles is known to do, and permit a lighting up of a lesion otherwise quiescent. The transition stages apparently existing between erythema nodosum, on the one hand, and erythema induratum and the tuberculids on the other, together with the experimental evidence cited, would seem to make this view the less probable one. The more probable one, in my opinion, is that which harmonizes with current conceptions of the etiology of tuberculids, that the purpuric, erythematous, and nodose lesions are cutaneous reactions to hematogenously distributed tubercle bacilli, deposited in a hypersensitive skin and originating in a tuberculous focus, sometimes unrecognized, perhaps for many

years. Whether the tuberculous phase is the cause or the consequence of the frequent clinical association of the cutaneous symptoms with the disease loses none of its importance from the standpoint of diagnosis and therapy.

2. Since the clinical appearance of the eruptions discussed does not, in my opinion, offer adequate means for differentiating "tuberculous" from non-tuberculous forms, every case of purpura, and many cases of erythema multiforme, should, I believe, be subjected to a preliminary survey for the possibility of tuberculous infection. Every case of erythema nodosum should be subjected to an even more searching examination.

3. The search for a focus of tuberculosis should employ the usual evidence elicited from the history, weight, and temperature curves and radiograms and physical examination for pulmonary and glandular signs (present in 8 out of 10 of the cases) here presented. The teeth and the nose and throat should be systematically examined for collateral foci of pyogenic infection, and dermatologic consultants sought for seemingly trivial lesions on the fingers, face, and legs, such as scars and pustular lesions on the trunk, macular pigmentation, etc., to say nothing of the more obvious cutaneous signs of tuberculosis, such as erythema induratum, papulonecrotic tuberculids, and folliculitis (present in 3 of our cases).

4. Cases of erythema nodosum, whatever their type, should be subjected to periodic reexamination and observation.

5. In the absence of a demonstrable source of pyogenic infection and even in its presence, the possibility of tuberculous etiology should be seriously entertained and an antituberculosis hygiene considered.

6. The results of the application of the foregoing principles and routine to the dermatoses mentioned, while only partial as yet, have shown so high a percentage of demonstrable and suspected tuberculosis—pulmonary and glandular, osseous and cutaneous, as to lead the writer to suspect that the association is more than coincidental, and that it can safely be made a basis for diagnostic and therapeutic decisions in a considerable percentage of cases.

7. It seems not improbable that erythema nodosum, especially, may be a syndrome of tuberculous as well as diphtheroid or streptococcal origin in an as yet unestablished percentage of cases.

8. Erythema induratum would seem to be susceptible of interpretation as, in a sense, a chronic ulcerative phase of tuberculous erythema nodosum, since intermediate types appear in this series.

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## II. THE DIAGNOSTIC AND CLINICAL RELATIONS OF CERTAIN TUBERCULIDS \*

The tuberculid is a cutaneous lesion of exceptional interest to the pathologist, the internist, and the general diagnostician. The term was devised by Darier to describe a group of lesions associated with tuberculosis of the viscera, which, while accompaniments of this disease clinically, did not exhibit necessarily the characteristic pathologic anatomy of tuberculosis in other structures. Thus, for example, lupus vulgaris is a true tuberculosis of the skin, with the histologic architecture associated with the disease in other parts of the body. The papulo-

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necrotic tuberculid, on the other hand, is a localized, non-specific of inflammatory reaction, the individual lesions being papules occurring by preference on the extremities, each distinguished by a central necrotic plug, which, on separation, permits the healing of the lesion with the formation of a punctate, atrophic scar. Upon the etiology of tuberculids a large amount of clinical and experimental work has been done. The relative degrees of association of the various types with tuberculosis have been widely studied. Lichen scrofulosorum, a group of follicular, papular eruption, has been clinically and experimentally demonstrated to be a tuberculid. The papulonecrotic tuberculid, another type of cutaneous lesion, is now generally accepted as of tuberculous origin, so that its use as a diagnostic criterion in the identification of tuberculous lesions, frank or occult, is justified by a large body of clinical and experimental evidence. Two types of papulonecrotic lesion with distinguishing characteristics are given separate names in the majority of dermatologic texts. These are acnitis, the papulonecrotic tuberculid of the face, first clinically defined by Barthélemy, and folliculiclis, the papulonecrotic tuberculid of the extremities. Of the two, the former is stated by Jadassohn to have the more distinctively tuberculoid histopathologic structure. A third type of tuberculid, one degree removed, so to speak, from final demonstration as a manifestation of tuberculosis in the skin, is the so-called erythema induratum of Bazin, a plaque-like lesion prone to ulceration, most often found on the lower extremities, especially the calf of the leg. The tuberculous character of this lesion, in spite of its inflammatory architecture, is now practically conceded, especially as a result of the recent rapid advances in methods of demonstrating the tubercle bacillus by animal inoculation, antiformin digestion, etc. It also is a lesion of marked diagnostic value in the recognition of obscure tuberculosis. A number of other lesions, for various reasons, are now held to be tuberculids, among which might be mentioned acne scrofulosorum, pityriasis rubra pilaris, certain exfoliative erythrodermias, acne necrotica, acne cachecticorum, lupus pernio, and the sarcoids. The possible tuberculous relations of lupus erythematosus and of purpura, erythema multiforme, and erythema nodosum are also subjects of recent and active discussion. The material of the Mayo Clinic seems to be exceptionally rich in tuberculids, and this has afforded a number of opportunities to study the clinical and diagnostic relations of those types now accepted as on a definitely tuberculous status—the papulonecrotic tuberculid and erythema induratum.

e. moreover, discussed 8 of the cases in the present series of 30 the standpoint of the relation of erythema nodosum to tuberculosis.\* The crux of the discussion of tuberculids among dermatologists and ophthalmologists has centered about their pathogenesis. This point was recently brought out in Jadassohn's masterly review of the subject before the war. It was also dealt with in a symposium before the meeting of the Dermatological Section of the American Medical Association (1918), the discussions to appear in the *Journal of Cutaneous Diseases* during the year. The problem of investigators has been to explain how a lesion, which in pathologic architecture is not tuberculous, can present such an unvarying association with a tuberculous focus as is to be found in the papulonecrotic and erythema induratum types of tuberculids. The theories on which work was at first conducted followed the familiar toxic lines, and ascribed the cutaneous lesions to tuberculotoxins elaborated at a distant focus. The development of experimental methods has, as already intimated, relegated this theory increasingly to the background and brought forward more and more convincing evidence that the tubercle bacillus itself, probably hematogenously distributed, is responsible for the individual lesions of a tuberculid. While organisms are exceedingly difficult to demonstrate in these tissues, positive results are claimed, and the percentage of successful animal inoculations is rising above the margin of experimental error for this mode of establishing tuberculosis. But the demonstration that the tubercle bacillus, whether in virulent or attenuated form, is responsible for the lesion is not adequate to explain why in one case hematogenously distributed bacilli gave rise to tubercles and epithelioid changes, and in others to merely non-specific inflammatory reactions with necrosis or to fibroid changes of a quasineoplastic instead of granulomatous character. In animal experimental work it has been shown that the tubercle bacillus can persist as an embolic invader in veins without setting up more than trivial changes (Liebermeister). Through the work of Saevcs in trichophytoses a similar condition of insusceptibility of tissues has been recognized in these diseases. One explanation, that of a difference in the virulence of the invading organism, has had numerous proponents. It has, however, gradually given place to an explanation based on the different reactivity of different persons, and even of different tissues to the organism. In other words, cutaneous allergy or hypersensitiveness has been invoked to explain why one person develops

\* Study I: "Tuberculous" purpura, erythema multiforme, and erythema nodosum.

lupus vulgaris, another a papulonecrotic tuberculid, another lichen a fulosorum, and still another, perhaps, a sarcoid. The importance of an allergic factor was effectively demonstrated in the experimental work of Rist and Rolland, and there can be little doubt that while its significance may be overestimated by some investigators, it is one of the best available explanations of the phenomena. For a fuller consideration of the experimental work underlying this theory reference should be had to

the studies of Gougerot, Rist and Rolland, and Zieler.

Thus far the principal emphasis has been placed on tuberculin and tuberculotoxins themselves as the agents that sensitize the tissues to the hematogenously distributed bacilli. Ingenious explanations have been devised to account for the observed failure of certain persons with tuberculids to react to tuberculin in the von Pirquet or intradermal tests. These follow the immunologic conceptions applied in explaining the failure of extreme stages of tuberculosis to react to tuberculin. Thus far, however, little account has been taken of the possibility that sensitizing agents other than



Fig. 218.—Acnitis, the papulonecrotic tuberculid of the face. Patient had had tuberculous peritonitis. Note the central necrotic plugs and the uniformity in size and age of the lesions. The crop appeared following quinsy, was treated as acne vulgaris, and was ascribed by the patient to nux vomica.

tuberculin may be responsible for a part of the allergy which makes a tuberculid possible, and that the person who does not react to tuberculin fails to do so because he does not owe his sensitiveness to tuberculin, but to some other toxic substance or bacterial product. This point will be raised again in pointing out the association of tuberculids with pyogenic foci of infection, as evidenced in this series. The mechanism of the allergic reaction which results in the formation of the papulonecrotic tuberculid is, roughly, as follows:

Bacilli are carried by the blood-stream to a hypersensitive skin and

ited at points where the circulation best favors the lodgment of tubercles—namely, in the extremities. At once a local anaphylactic reaction is set up, an inflammatory papule forms, and at the point where the reaction is most intense disintegration of the tissues occurs, central necrosis. In the reaction the organisms which precipitated the lesion are largely destroyed, which accounts for the excessive rarity of their demonstration. The pathologic picture is that of an acute inflammation, is practically identical in the papule of a von Pirquet reaction, the lesions of folliculitis or acnitis, and the lesions of erythema induratum. While a tuberculid may be tuberculosis cutis histologically, it is due to the presence of the tubercle bacillus, and as such is evidence of its presence in the body. This, in effect, summarizes the trend of modern opinion. It should not be forgotten that, in all generalizations, this one is its borderline, and that it is possible to demonstrate lesions which clinically are tuberculids, but which have the architecture of tuberculosis (Harris' case of dermatitis nodularis necrotica, as illustrated in Pusey's "Principles and Practice of Dermatology").

Tuberculids of the papulonecrotic and erythema induratum type, when recognized, have a considerable value to general diagnosticians as earmarks of obscure tuberculosis. An understanding of their pathologic and clinical background often throws much light on the elements in the patient's general condition, which may be ignored or misinterpreted. A preliminary description of the type here considered will be of assistance in a comprehension of these relations.

It must be borne constantly in mind that the distinction between types of papulonecrotic tuberculids, that is, folliculitis, the papulonecrotic tuberculid of the hands, or acnitis, that of the face, is largely for clinical



Fig. 219.—Acnitis, the papulonecrotic tuberculid of the face in a patient with tuberculous adenitis, showing the involvement of the ear by the tuberculid. The black spot in the helix is an active lesion. "Moth-eaten ear."

convenience, and that one is not exclusive of the other. All the forms may be present at the same time in the same person or in succession at different periods of his history. The identification of the elementary lesion of a tuberculid, or in fact of any dermatosis, is the requisite to a diagnosis. The elementary papulonecrotic lesion is exactly what its name indicates: Whether occurring on the face, the hand, the buttock, the legs, the toes, the ears, it is an inflammatory papule exhibiting, in fully developed form, a central necrotic plug of tissue usually dark in color. In its earlier stages the papule may vesiculate



Fig. 290.—Various types of folliculitis, the papulonecrotic tuberculid of the hands. An active lesion on the fourth finger of the left hand. Note the typical crater left on removal of the necrotic plug. Patient with tuberculous arthritis.

later drying enough to show the necrotic plug. The plug may, in the later stages of the lesion, either suppurate out, or be picked out by the patient, leaving a conic depression which heals, producing a punctate, atrophic scar. The inflammatory process which produced the papule also gives rise to a ring or collaret of hyperpigmentation about the scar, which persists for periods of months or even years in certain situations, especially on the lower extremities, where stasis accentuates the process. A papulonecrotic lesion may vary in size from a large pinhead in folliculitis to a pseudofuruncular lesion several centimeters across in

atitis nodularis necrotica, but if careful examination is made, the active or essential lesions can usually be found.

Failure to recognize papulonecrotic lesions or their scars is quite as much due to faulty methods of examination as to unfamiliarity with the condition. The localizations and sites of predilection of the lesions are not inspected by the internist, who is interested in percussing the chest or palpating the abdomen. Instead of making a purely objective examination of the entire body, the busy diagnostician, guided by the history, is likely to overlook the moth-eaten ear of acnitis unless he is expecting gouty tophi. In the same way the backs of the terminal



Fig. 221.—Folliclis in a patient with erythema induratum. Note the various stages—a fresh papule on the patient's right little finger, vesicle formation, and beginning necrosis on the left little finger, active lesions with central necrosis on the right index and middle fingers, scars on the left index and middle fingers.

phalanges and the tips of the fingers, the favorite localization for the form of papulonecrotic tuberculid known as folliclis, are seldom the subjects of painstaking inspection by general diagnosticians. Punctate atrophic scars about the elbows and the extensor surfaces of the forearms are attributed to furuncles and trauma, instead of to the tuberculid responsible for them. A poor light as well as cursory inspection is responsible for many misconceptions of these lesions. Surprising and entirely unwarrantable operative interference may be practised on tuberculids of the leg through insufficient observation or faulty interpretation. Incisions for drainage, excisions with suture, skin-grafts, and transplants, excisions for diagnosis, with a report of "fibroma,"

"inflammatory tissue," etc., are frequent. The exquisite tenderness of many of the larger leg lesions combined with central softening misinterpreted as osteomyelitis or furunculosis, and subjected to operative trauma.

Erythema induratum is in a sense only an exaggeration of the papulonecrotic lesion. In fact, the larger lesions often seem to be produced by a confluence of smaller nodes. The typical lesion is an erythematous to violaceous plaque, usually several centimeters in diameter, firm, indurated, and somewhat tender. By predilection these lesions are said to appear on the posterior aspect of the leg, in the region of the calf.



Fig. 222.—Follicles localizing at points of greatest trauma. Patient with tuberculous gland.

and ankle, but this localization, in my experience, is by no means constant. Lesions varying all the way from the small necrotic centered papule, through the breaking-down nodule to the typical ulcerative plaque, may be found scattered about the lower, and at times even the upper, extremities. In fact, the presence of papulonecrotic lesions is a material aid in diagnosis of a solitary ulcerative plaque of erythema induratum.

The scars of tuberculids are in many ways quite distinctive. This is especially true if their distribution is limited to one or the other of the sites of predilection. A number of these sites, with their character-

lesions and scars, are illustrated in Figures 218–225, 228, 229, 232, 235, and 237. The scar is never contractile or distorting, and a peculiar punctate atrophy produced may suggest that of a variolous scar, although it is usually deeper.

#### SUMMARY OF DIFFERENTIAL DIAGNOSIS

*Papulonecrotic tubercle of the face—acnitis* (Figs. 218 and 219).—This lesion is to be distinguished from *acne vulgaris* by the circumscribed



Fig. 223.—Faceted, grouped scars of folliculitis, index, middle (tip), and fourth fingers. Vasomotor abnormalities, tuberculous adenitis.

a papule with central necrosis, as distinguished from a pustule or infected comedo, and by the uniformity of the lesions, which tend to appear in crops and hence to be, to a considerable extent, of the same age and size. The moth-eaten ear, due to papulonecrotic lesions in this site, is illustrated in Figure 219. The absence of comedones and seborrhea and of transition lesions from comedone to pustule is significant. Acute acnitis may strongly suggest variola, from which its course distinguishes it.



nodules of Hodgkin's disease may suggest a tuberculid, but their intensely pruritic character and the multiple evidences of scratching, including the history of violent itching, together with the absence of central necroses, eliminate the tuberculid. The nodules of Hodgkin's disease do not primarily localize on the extremities. I have known a generalized tuberculid to be diagnosed a psoriasis in the presence of marked crusting, the diagnostician forgetting that psoriasis does not produce scars.



Fig. 226.—Serpiginous ulcers produced by the confluence of solitary nodules and plaques. Scar of unwarranted surgical interference on the left leg.



Fig. 227.—Solitary gummatous ulcer with edema and infiltration of the surrounding tissue, to show the differential points.

*Papulonecrotic tuberculids of general distribution* (Fig. 222).—These lesions may occur in showers, especially involving the trunk. Their tendency to show a vesicular stage and the necrosis as distinguished from pustulation help to eliminate a pustular syphilid. The diagnosis of this type of lesion may offer great difficulties, and not infrequently the conclusion must depend on collateral evidence of the presence of tuberculosis and the absence of syphilis and on recurrence and chronicity. One such case in my series yielded a positive Wassermann reac-

tion on several occasions, and only the recurrence of the lesions through a period of years and the final occurrence of typical necrotic papules made the differentiation possible. The scars of a widely distributed tuberculid may suggest those of a pustular syphilid so strongly that serious mistakes may be made. In one such case a positive Wassermann and a mass of glands which cleared under arsphenamin seemed to establish a diagnosis which was reversed by later findings.

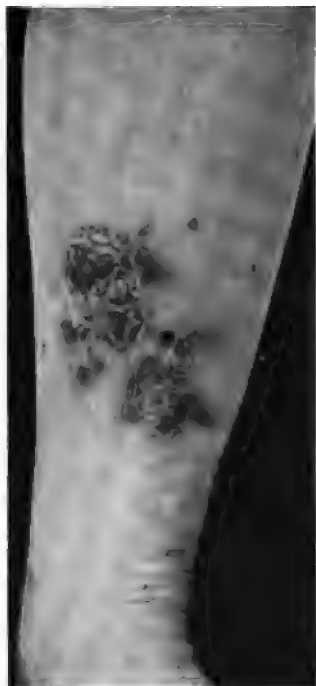


Fig. 228.—Erythema induratum with papulonecrotic lesions on the legs of a patient of the "occult" type.



Fig. 229.—Same as Fig. 228.

There is a distinct tendency for papulonecrotic tuberculids to occur at points of trauma. This fact has, in my experience, led to confusion with epidermolysis bullosa hereditaria, especially when lesions were localized on the elbows. One distinctive site of lesions in epidermolysis bullosa hereditaria, over the thyroid cartilage of the larynx from collar trauma I have never known to be the site of tuberculids not involving the face. Moreover, the bullous phase of epidermolysis is much more marked than the vesicular phase of tuberculids, which is often abortive.

Nevertheless, the scarring produced by the two conditions may have many points of similarity (Fig. 223).

*Erythema induratum*.—This condition seldom occurs alone. It usually is associated with papulonecrotic lesions that may group to form larger plaques. The differentiation from nodular lues depends first on the tendency of the lesions to symmetric distribution on both



Fig. 230.—Scars and pigmented residua of *acne scrofulosorum*, the papulonecrotic tuberculid of the trunk in a patient with tuberculous adenitis. Note lesions on the extensor surfaces of the forearms also. This patient also had lesions of follicles on the fingers.

extremities, and, second, on the multiplicity of the lesions and their lack of configuration, that is, their irregular shape and arrangement as distinguished from the grouping into typical arciform or polycyclic arrangements observed in lues. The scars exhibit the same peculiarities (Fig. 224). From gumma of the pretibial region the solitary character of the gumma and the preference of erythema induratum for the posterior surface distinguish it. It should be remembered, however, that gummas may also be symmetric and multiple. Multiple infarctions in the skin or anemic ulcers are usually only associated with high degrees of thrombotic occlusion of the veins, which can be seen and palpated, and with suggillation and

hemorrhage into the skin and even multiple areas of gangrene. Erythema nodosum is usually distinguished from erythema induratum by the tendency of the latter to ulcerate and to occur by preference on the posterior surface. As a matter of fact, all stages in the transition from erythema nodosum to erythema induratum, as regards both morphology and localization, may be seen in subjects with a tuber-

culous background, so that some of the distinctions are artificial. Streptococcal or diphtheroid erythema nodosum of the Rosenow type, however, does not ulcerate, and the process is, in general, more acute, the nodes more brawny and edematous, and the hemorrhagic and ecchymotic changes and edema more marked than in the tuberculous type. A résumé of this aspect of the problem may be found in the discussion of tuberculous erythema nodosum in the first study of this series.



Fig. 231.—Characteristic scarring and active lesions of the papulonecrotic tuberculid on the elbows of a patient with tuberculous adenitis.

Ulcerative erythema induratum is to be differentiated from nodulo-ulcerative syphilids again by its tendency to symmetry, which, however, is no more invariable than is asymmetry in lues. The luetic ulcer has a configuration which can be recognized by practice as segmental or arciform. The erythema induratum ulcer is irregular and

nondescript. Instead of a sharp margin closely bordered by normal skin, the erythema induratum ulcer is usually undermined, has a grumous, or hemorrhagic discharge, and is surrounded by bluish serous dermatous sodden tissue. There is usually no definite gummatous slough, as in lues. The concomitant occurrence of papulonodular lesions and nodules greatly assists in the recognition of erythema induratum. The typical chronic varicose ulcer is easily differentiated by its rigid scar tissue border, its flat, open floor of anemic granulation

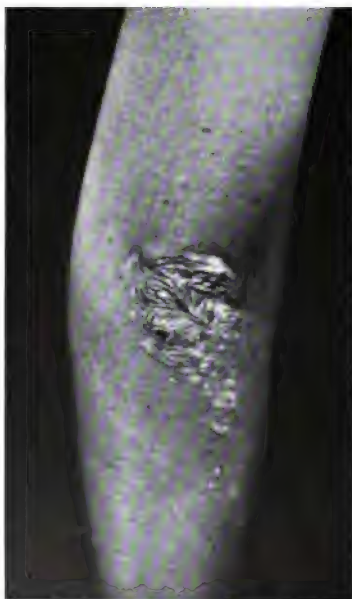


Fig. 232.—Tuberculid scarring on the elbows.



Fig. 233.—Scarring about the elbow of a patient with epidermolysis bullosa hereditaria.

and the usual regularity of its margins. Epithelioma is usually unilateral and has a highly characteristic nodular and rolled, pearly margin.

A word of warning should be given as to the use of arsphenamine in an attempt to make a differentiation between a tuberculid and a syphilitic lesion by therapeutic test. Tuberculids, as will be seen in a subsequent paper, respond rapidly to this form of medication, so that a false therapeutic effect is produced which may subject the patient to prolonged treatment for a non-existent lues.

### ICAL RÉSUMÉ OF THIRTY CASES OF PAPULONECROTIC TUBERCULID AND ERYTHEMA INDURATUM

The series of cases collected by the writer during the past two years rates in a convincing way the association of these conditions with reulosis. Of the 30 cases, 80 per cent were women. This preference of women over men has been recognized by others. In a s of 100 cases of tuberculous adenitis reviewed in connection with



Fig. 234.—Types of scarring on the lower extremities. Epidermolysis bullosa hereditaria—the same patient whose elbow appears in Fig. 232.



Fig. 235.—Scarring of a rather large papulonecrotic tuberculid on the calf of the leg. Note the multiplicity of lesions, lack of configuration, peripheral hyperpigmentation. Patient with tuberculous adenitis and arthritic symptoms.

this study a similar proportion of 64 per cent women and 36 per cent men was observed. The youngest patient was ten years of age, the oldest fifty-one. Of 13 cases in which data were available, the onset of the tuberculid had been in the second or third decade of life in 12, corresponding in this particular to the period of greatest incidence of signs of systemic tuberculosis.

Eighty-three per cent of the 30 patients bore evidence of past or

present lesions of the papulonecrotic type. Three had lesions on the face (acnitis), 12 had lesions or scars on the hands (folliculitis), 12 had papulonecrotic lesions on the legs, and 9 had them on the trunk. Of the 2 patients presented an erythema induratum uncomplicated by any tuberculid. One of these had apparently a tuberculosis verrucosa cutis and the other had undoubted tuberculous adenitis. It is apparent that in its association with other more definitely proved tuberculous lesions in this series, erythema induratum establishes still further its claim to tuberculous origin.



Fig. 236.—Hyperpigmentation and scarring due to papulonecrotic lesions on a stasis leg. Patient also had folliculitis on the fingers.



Fig. 237.—Scar of a healed stasis ulcer due to erythema induratum on the lower portion of a leg.

#### RELATION OF THE CUTANEOUS LESIONS TO SYSTEMIC TUBERCULOSIS

*History of tuberculosis in the family or patient.*—A definite history of tuberculosis in the family, sufficiently direct to bring the patient into contact with it, was given by one-fourth of the cases (23 per cent). Somewhat more than one-third of the patients had been diagnosed as tuberculous previous to their examination in the clinic. The diagnosis was usually based on adenopathy rather than on pulmonary or other signs.

*the objective manifestations of tuberculosis.*—It is to be understood tuberculids as signs of tuberculosis are excluded. Fifty-seven per cent or more than half of the entire series, showed incontrovertible objective signs of tuberculosis, usually in such numbers that any one sign been insufficient, the others would have confirmed the diagnosis.

Thirteen per cent of the cases were rated as disputable, and 30 per cent presented no definite signs. Table 1, summarizing the disputable occult cases, is here appended:

TABLE 1  
DOUBTFUL CASES

- Case A202732.—Erythema nodosum; loss of weight; doubtful lung lesion, as revealed by x-ray and physical examination.
- Case A212370.—Tenosynovitis, tuberculous? (folliclis, erythema induratum).
- Case A188556.—Erythema nodosum and erythema multiforme. Enlarged right cervical glands; temperature and lung signs.
- Case A224920.—Family riddled by tuberculosis; patient under weight; asthenic, well-defined signs in right apex (folliclis, fingers and toes).

OCCULT CASES

- Case A39183.—Obscure anemia; inflammatory changes in abdomen; positive and negative Wassermans at various times; menorrhagia; headaches; generalized papulonecrotic tuberculid.
- Case A197825.—Florid, obese girl; no signs of tuberculosis; erythema induratum.
- Case A221958.—Positive Wassermann without history or evidence of syphilis; lupus erythematosus of the face; folliclis, scars on fingers.
- Case A218528.—Anemia, persistent; marked loss of weight; erythema induratum and papulonecrotic tuberculid of the legs.
- Case A201284.—Anemia, pernicious (?); extreme hyperpigmentation; cachexia; tuberculid of the legs; lupus erythematosus; adrenal tuberculosis (?).
- Case A171947.—General examination negative; obese, well-nourished woman; extensive papulonecrotic tuberculid of the legs with erythema induratum.
- Case A63167.—Iritis in childhood; tuberculosis of the knee(?); three weak positive Wassermans without evidence of lues; alveolar abscess, otherwise negative; papulonecrotic tuberculid of legs and elbows; erythema induratum.
- Case A186129.—Repeated positive Wassermann; exposure, but no evidence of lues; folliclis of hands; scars of papulonecrotic tuberculid of the body.
- Case A233765.—Obese girl; no signs of tuberculosis, but von Pirquet strongly positive; erythema nodosum and induratum; legs and arms involved with purpuric lesions.

The occult cases form a group of special interest. The mere fact that a gross focus of tuberculosis cannot be demonstrated is, of course, not an evidence that such a focus may not exist, in the retroperitoneal glands, for example, or in the uterine adnexa.<sup>6</sup> Two of our patients gave histories suggestive of such a focus, but in the absence of operative exploration the focus could not be demonstrated. Four of the nine occult cases were in florid, rather obese persons, of a type recognized as predisposed to some extent to tuberculous infection.



One-third of 27 cases in which radiograms of the thorax were made showed evidence of pulmonary tuberculosis. The involvements were largely apical, with calcification and signs of healing in several. The importance of a tuberculid as a diagnostic lead for the internist can be appreciated from such a finding. Four cases showed doubtful x-ray signs of little independent value. One-third of the cases likewise presented physical signs suggestive of pulmonary tuberculosis. Both physical and x-ray findings were present in 5 (17 per cent) of 29 cases.

More than two-thirds of the patients had a visible and palpable lymphadenitis, making glandular involvement the commonest form of

tuberculosis associated with these tuberculids. In 38 per cent the adenitis was marked. This very evident association of tuberculids with glandular tuberculosis forms a theoretic basis for explaining their presence in occult cases without visible manifestations. Moreover, the association of tuberculids with a form of tuberculosis that, in a broad way, indicates a high individual resistance to the bacillus is of interesting prognostic significance, and suggests that a tuberculid, among other signs, may be in a way accepted as



Fig. 238.—Scar of a nodule—ulcerative syphilid of the pretibial region. Note the arciform, polycyclic configuration.

evidence of a benign course of the disease. This point is of interest in connection with the older conceptions of the extreme gravity of the papulonecrotic tuberculid in infancy. A recent study by Hempelmann has brought forward evidence to show that even in infancy the association with lymphatic tuberculosis (tracheobronchial node involvement) can be recognized, and that the prognosis in cases with tuberculids is no graver than in those without.

Among other forms of tuberculosis with which tuberculids in this group were associated the following should be mentioned: sacro-iliac abscess, tuberculous peritonitis, renal tuberculosis (bacilli demonstrated), and tuberculosis verrucosa cutis, one case each; tuberculous keratitis,

3 cases. In one patient the tuberculosis verrucosa cutis occurred on the right leg, the erythema induratum on the calf of the left.

*Prevalence of tuberculids in connection with tuberculous glands.*—In endeavoring to ascertain the prevalence of tuberculids in cases of tuberculous adenitis, as observed by internists in the material of a large clinic, 100 cases of tuberculous adenitis were reviewed for evidence that any cutaneous lesion had been observed. In this series 10 per cent were described as having lesions which could be inferred to be tuberculids. The proportion of men to women among those having cutaneous lesions was as 1 to 10, which is not far removed from the percentage observed in the series of tuberculids under discussion. There can be little doubt that a number of the less obvious tuberculids were overlooked and that 10 per cent is too small a figure for the incidence of these lesions in glandular tuberculosis.

A careful comparative study of the cutaneous lesions and the types of tuberculous systemic involvement failed to reveal any constant relation between the tuberculous focus and the type of tuberculid. On the other hand, a definite relation between vasomotor and stasis phenomena and the distribution of the tuberculid was apparent. There was also evidence to show that the more extensive tuberculids in a rough way were associated with what seemed the more extensive and serious types of systemic tuberculous involvement. Seven of the 9 cases presenting extensive tuberculids involving trunk and extremities also presented the most serious forms of tuberculous involvement in the series.

#### RELATION OF VASOMOTOR PHENOMENA AND VASCULAR STASIS TO THE DISTRIBUTION OF TUBERCULIDS

It has long been recognized that a tuberculid tends to appear on the extremities, and especially to appear in those patients in whom the peripheral circulation is feeble or obstructed. Data on the collateral local vascular findings were collected on 28 cases in this series. Of these one-half (50 per cent) showed abnormalities of the vascular supply in the form of cyanosis and vasomotor anomalies of the extremities, and swollen hands, legs, or feet. Every "stasis leg," that is, one with a tendency to passive congestion from defective venous return, had erythema induratum. Five of 7 with blue hands had folliclis. The possession of a leg with a tendency to vascular stasis thus predisposes, to the extent of nearly 100 per cent, to the type of tuberculid known as erythema induratum. In the same way the possession of cold, clammy,

mottled hands predisposes to the extent of more than 70 per cent the development of folliclis. It was a matter of note that all the patients who, at the onset of their cutaneous lesions, had been overweight showed the severest part of their manifestations in the lower extremities, a fact which accords well with the vascular stasis usually present in the legs. Obese persons, therefore, seem to be predisposed to the erythema induratum type of tuberculid, and the thin and neurotic, with marked vasomotor imbalance, to folliclis. Only 2 of 7 obese patients had folliclis and one of these was a child with a generalized tuberculid.

Summarizing the series as a whole from the standpoint of location of lesions, more than half (57 per cent) of the patients had lesions on the upper extremities, but almost three-fourths (74 per cent) had them on the lower extremities, showing the distinct predilection for parts of slower circulation. Ninety-six per cent of the patients, or practically all, had lesions on either upper or lower extremities. Twenty-three per cent had lesions on the upper extremities and not on the lower, 43 per cent on the lower and not on the upper, so that the odds are 2 to 1 in favor of the lower extremity as a site of involvement. One-third had involvement of both extremities, one-third showed involvement of the trunk, and one-fifth of the face. It is of interest to note that 65 per cent of those in whom the face was involved had lesions on the ears, and that the ear was the seat of lesions in 13 per cent of the whole series.

The importance of the circulatory factor in the distribution of tuberculids is one of the strongest arguments for the bacillemic as opposed to the toxemic origin of the process. The presumption is that at points where the circulatory stream is moving most slowly the maximum opportunity for the deposit of organisms will present itself, and that lesions will tend to appear, as they do, in areas where one factor or another acts to delay the movement of the blood.

#### MISCELLANEOUS FINDINGS ON EXAMINATION

In the study of this series of cases a number of interesting miscellaneous findings developed. The recognition of concomitant tuberculous in cases exhibiting a tuberculid is, on the whole, a matter of identifying signs by objective examination rather than of eliciting symptoms. Six of the patients had a temperature of 99° or over at the time of examination, although temperature is a much more important factor at onset, especially in those cases which begin as erythema multiforme.

**erythema nodosum.** Of a series of 7 such acute cases, 5 showed temperatures varying from 99° to 103°. Cough had been a well-defined symptom in only 7 of 25 cases, or less than one-third; night-sweats were present in none; sputum in only 2—both negative for bacilli. On the other hand, amenorrhea was a definite symptom in 43 per cent of the cases, and in some was coincident with the greatest activity of the tubercle bacillus. Losses of weight varying from 2 to 45 pounds occurred in 60 per cent, more than half losing less than 10 pounds.

The periodicity of tuberculids and their tendency to exacerbation during spring and fall, which is an important factor in treatment and an aid in diagnosis, were apparent in nearly half of 20 cases in which data were obtained. More than three times as many recurred in spring as in fall, and one-fourth of the patients had lesions continuously.

A little less than half the cases presented secondary anemias with a hemoglobin below 70 per cent (Dare). In one-fourth of the cases it was below 53 per cent, the lowest being 30 per cent. In the latter case a possibility of a pernicious anemia was entertained. From two of the anemias the influence of syphilis could not be eliminated. Accompanying the anemia was a tendency to leukopenia. Even in the acute cases the patients did not, while febrile, exhibit any tendency to leukocytosis. Thirteen of 25 patients had counts below 6600, 8 below 5800. Only 3 exceeded 10,000. No differential counts were taken. On the score of blood-pressure, 35 per cent were below 120, the lowest 98; 40 per cent were normal, and 25 per cent exceeded 135 systolic, the highest being 142. The higher pressures were all in persons under thirty-one. The diastolic and pulse pressures exhibited no distinctive variations. Observations on the Wassermann test in the tuberculids will be included in the discussion of allergic manifestations.

It is apparent from this review that the clinical accompaniments of a tubercle bacillus tend to be those of a low-grade tuberculous infection. A moderate secondary anemia and leukopenia, with occasionally an afternoon temperature, most likely to appear during exacerbations; moderate loss in weight; occasionally cough associated with a lighting-up of the acute process, and signs of a definite but not fulminating process in the lungs or glands, makes up the average clinical picture in a large percentage of the cases. The florid type of case must constantly be borne in mind in dealing with tuberculids, and mere robustness, weight, and color must not be accepted as invalidating a diagnosis based on the tubercle bacillus.

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## THE TUBERCULID IN DIAGNOSIS

While some caution must be exercised in inferring the diagnostic career of a case from the patient's history or examination, such a study of our series of cases suggested several points of interest. In only 1 of the 30 cases referred for diagnosis to our department had a correct diagnosis been made, and tuberculosis on the score of their cutaneous manifestations had not been suspected. In 2 of the 5 cases the diagnosis might have been made by the internist, but was later made by a dermatologist before the patient was seen by us. In more than one-third of the cases the tuberculid had either been overlooked or ignored as insignificant. This was especially true of acnitis on the face and folliculitis on the fingers. In another third of the cases the cutaneous lesions had been misdiagnosed, to judge from the history or treatment. Six of the 9 cases in this second group had been interpreted as syphilitic, because of the finding of a positive Wassermann, a point to be discussed in connection with allergy. Two were interpreted as luetic because of the history of what was probably a general or extensive shower of tuberculid lesions, of which the scars were present. Another point which seemed to suggest lues was the history of arthritis, myalgia, and indefinite pains with mild anemia often given by these patients. Six cases, or one-fifth of the series, had sustained probably needless operative procedures in the effort to make a pathologic diagnosis from the lesions, or for excision, curettage, or drainage. The vasomotor and stasis factors had led to a diagnosis of Raynaud's disease in one case, and varicose ulcer in another. One, because of lesions on the elbows, in spite of obvious scars, sustained a diagnosis of psoriasis.

It is apparent that unfamiliarity with the lesions and failure to observe, whether due to poor light or other cause, together with the tendency to interpret a tuberculid as syphilis, account for four-fifths of the diagnostic errors. For the former difficulty the remedy is obvious. For the latter it should be recalled that not all skin lesions that occur in the presence of a positive Wassermann reaction are syphilitic, and that the recognition of syphilis does not remove the obligation to ferret out an associated tuberculosis, particularly when the cutaneous evidence points toward it. The occurrence of false positive Wassermann reactions from cholesterinized antigens in the presence of tuberculosis and the absence of syphilis is also being gradually established. The occurrence of tuberculids in crops, their wide distribution on the face, trunk, and extremities, and the frequently associated myalgias and arthralgias

the points in the history which seem to suggest lues and septic foci rather than obscure tuberculosis to the casual mind. The usefulness of tuberculin in determining the character of an adenopathy was attended in several cases in which internists had estimated the diagnostic probabilities of cases at 30 to 70 per cent in favor of Hodgkin's disease, asked for excisions for diagnosis before seeing the report of the pathologist.

TABLE 2.—HISTORY OF ACUTE INFECTIONS

CASE	TONSILLITIS	RHEUMATISM	PNEUMONIA	GRIP	PLEURISY
29	X	..	..	X	..
32	..	..	..	X	..
29	X	X	..	..	..
33	X	..	X	X	X
70	X	X	..	..	..
150	X	X	X	X	..
847	..	..	..	X	..
350	X	X	..	X	X
923	..	X	X	..	..
183	..	..	X	..	..
356	..	..	..	X	..
425	..	X	X	X	..
1938	..	..	..	X	..
4673	..	..	..	X	..
8021	X	..	..	..	..
9238	..	X	..	..	..
4920	X	..	..	..	..
8772	X	..	..	X	X
18528	..	..	..	X	X
11592	X	..	X	..	..
91446	X	X	..	..	..
01284	..	..	..	X	..
71947	..	..	..	X	..
63167	..	X	X	..	X
20740	..	X	..	..	..
26884	..	X	X	..	..
23765	..	X	..	X	..
234128	..	X	..	..	..
Total	11 39 per cent	13 46 per cent	8 29 per cent	15 54 per cent	5 18 per cent

### THE COLLATERAL INFECTION FACTOR: ANAMNESIS

One of the most interesting relations brought out by this clinical study of the tuberculids was that of collateral types of infection shown in the history and in the examination. In the histories of these patients five syndromes stand out with overwhelming prominence. These are tonsillitis and "rheumatism" and pneumonia, grip, and pleurisy. The extraordinary prevalence of these two types of infections, representing



the focal infections traceable to tonsillar and alveolar pathology. In the respiratory group may be seen in Table 2. Since the records of these cases were taken by men who had no conception of a causal relationship between the dermatosis and the systemic condition, they are probably quite unprejudiced.

Summarizing Table 2, it appears that of 28 patients, 39 per cent had tonsillitis and 46 per cent had had rheumatism. Twenty-nine per cent had had pneumonia, 54 per cent had had grip, and 18 per cent had had pleurisy. Nearly 70 per cent had had tonsillar infections or rheumatism; 62 per cent had had definite respiratory infections, not including pleurisy.

TABLE 3.—APPARENT ETIOLOGIC CONNECTIONS

- CASE 186129.—Outbreak of general papulonecrotic tuberculid in the spring, following a winter of repeated tonsillitis and colds.
- CASE 169350.—Five years of rheumatoid pains. Grip followed by pleurisy and alveolar abscess; symptoms two years previous to examination; loss of weight, then outbreak of a papulonecrotic tuberculid. No improvement from tonsillectomy.
- CASE 154673.—Grip; while recovering, purpura and a papulonecrotic tuberculid.
- CASE 188556.—“Cold” with temperature, erythema nodosum, marked glandular enlargement on the right side of the neck, signs over right apex.
- CASE 197425.—Pneumonia, 1914; “rheumatism,” 1914–1917; then grip and an outbreak of erythema induratum.
- CASE 212370.—Tonsillitis, followed by tuberculid, rheumatism, hydrarthrosis, tenosynovitis; tonsils removed without benefit; appendectomy no effect; cleared up under treatment for the tuberculid. Teeth negative.
- CASE 191446.—Folliculitis for many years following tuberculous peritonitis. Quinsy three months previous to examination, followed by an abrupt outbreak of arthritis in addition to the folliculitis. Alveolar abscess.
- CASE 230740.—Pneumonia, 1913; axillary glands then enlarged; removed in 1916, incidentally with onset of tuberculid.
- CASE 174925.—Pneumonia sixteen years previously, followed by enlarging glands, removed by operation nine years later. Removal of the glands was followed by severe rheumatism, continuous up to present time. Tuberculid appeared one year after operation; glands recurred.

By the term “rheumatic symptoms” in the foregoing discussion is meant the group of myalgias, neuritides, arthralgias, and occasional arthropathies which do not fall definitely into the category of acute articular infections. So striking has been the association of this nondescript group of symptoms with the tuberculids that it is now our practice, in addition to the routine search for a focus of pyogenic infection in tonsils or teeth, to ray the chests of patients who, in association with suspicious eruptions, complain of “rheumatism.”

#### THE COLLATERAL INFECTION FACTOR: FINDINGS

*Examination of the tonsils.*—Data on the clinical condition of the tonsils were available in 21 cases of the 30. It is to be regretted that no

ologic examinations were made in those patients who sustained tonsillectomy while they were under observation. The information derived from clinical examination by an otolaryngologist was briefly as follows:

An exceptional degree of tonsillar infection seemed to prevail in the series as a whole. One-half of the patients were rated as having severe and badly infected tonsils. The other half were passable and borderline cases. Practically none were entirely within the limits of normality. On the other hand, curious contradictions seemed to exist in the picture. Almost an inverse ratio appeared to prevail between the condition of the tonsil and the severity of the tuberculid. Certainly there was nothing to indicate that the severe tuberculids were directly associated with severe tonsillar infection as seen on purely clinical examination. To confirm this evidence of the absence of direct causal relation between tonsil and tuberculid it appeared, moreover, that:

1. The tonsils in patients with tuberculous signs were no worse than those without. They would have been worse in the latter if they were to play the sole etiologic rôle.
2. No one tuberculid seemed to bear any special relation to the condition of the tonsils.
3. The tuberculid appeared after tonsillectomy in 3 instances.
4. Tonsillectomy performed in 7 instances failed to prevent or modify the course of the tuberculid.

In the light of these considerations it would appear that there is an indirect relation between infected tonsils and the presence of tuberculids, but no direct relation, both in the history and examination. In other words, the septic tonsil is probably not the tuberculous focus. If it is a factor in the situation, its more probable rôle is that of a predisposing or contributing factor.

*Examination of the teeth.*—This very important examination was not begun as a routine, unfortunately, until comparatively late in the series, when, in studying the clinical picture, the frequent occurrence of a secondary focus became apparent. The results of an examination of 9 cases by x-ray showed alveolar abscesses in 3 and a rarefying osteitis of the alveolar process in one. The presence of definite dental pathology in 45 per cent of the few patients examined is highly suggestive. It should be emphasized that gross examination of the teeth may afford no clue to the condition beyond the suspicions aroused by dental work which is founded on devitalized teeth. That the alveolar focus is not

the leading factor in the production of a tuberculid is again evidenced by the fact that it is not invariably present, and that in two cases (in which the teeth were normal to examination and tonsils were out of one of the two even the appendix was removed) the tuberculid and accompanying arthritic manifestations, including a tenosynovitis, remained unaltered until the institution of measures directed against actual or presumptive tuberculous focus.

It should not be forgotten that the search for a secondary focus in connection with a tuberculid should not terminate with tonsils and teeth. In one of our cases the history and findings suggested an infected gallbladder as a focus, although the teeth were negative and the tonsils were only moderately involved.

#### THE POSSIBLE BEARING OF CERTAIN ALLERGIC PHENOMENA ON THE ETIOLOGY OF TUBERCULIDS

Reference was made in the earlier part of this paper to the growth of a body of clinical and experimental evidence in support of an allergic factor in the etiology of tuberculids. As the prime exciter of the cutaneous allergy theoretically necessary to produce the non-specific type of reaction represented by tuberculids, tuberculotoxins have been accepted by investigators, apparently with whole-hearted enthusiasm. Undoubtedly their rôle is an important if not the major one. This enthusiasm has for the time being excluded from the field of vision other agents besides tuberculotoxins, which are able to excite a non-specific type of cutaneous allergy. For some years the cutaneous allergy of late syphilis (*Umstimmung*), for example, was regarded as highly specific, and the enthusiasm with which luetin was received and used was evidence of this uncritical point of view. It was not until certain observers, somewhat more skeptically inclined than the average, such as Boas, began to note the behavior of the skin to controls for luetin, that a field was opened for a non-specific interpretation. Sherrick's observation that the allergy of late lues, as evidenced by reactivity to luetin, could be artificially produced by the administration of potassium iodid was a major contribution. In 1916 I argued, on theoretic grounds, that the behavior of luetin was not due to the spirochaetes which it contained, but to an adsorption complex in which agar, the culture-medium, probably played a principal rôle. Acting on the theoretic considerations then presented, I succeeded in showing that agar in proper concentration makes an entirely satisfactory substitute for luetin in the luetin test.

plied to late syphilis, and that accordingly the reaction and the **gy on which** it depended were alike non-specific. In the course of **study of this phenomenon** I was able to demonstrate that an allergy **cally similar** to the non-specific allergy of syphilis could be artificially **luced by** the intradermal injection and lysis of even an autogenous homologous protein. In this experimental work I employed an **alsion of normal skin**, both my own and that of my assistant. As a **ult apparently** of a series of injections of this allergy-producing protein **assistant and I developed** a reactivity to agar which in all respects **itated the allergy** of late syphilis. This is essentially an experimental **rof of the fact** that cutaneous allergy of some types, as observed in a **ease such as syphilis**, can be artificially imitated by the intradermal **roduction of other proteins** than those of the specific organism of the **sease**. While it is not offered as adequate explanation of the allergic **enomena in tuberculosis** as manifested in the development of tuberculids, it is at least suggestive of the idea that proteins other than **tuberculoxins** may be responsible for the allergy that makes tuberculids possible. Such proteins may, in the light of the foregoing clinical **bservations**, be staphylotoxins and streptotoxins, derived from what I **ave called** the secondary focus observed in these cases. It is not impossible that the lysis of such toxins in the body, or even of the bacteria **themselves in recurrent bacteremias**, may so sensitize the skin that an embolus of tubercle bacilli will provoke a violent inflammatory reaction of a wholly non-specific character, precisely as agar does in the hypersensitive skin of late syphilis. The allergic specificity of the tuberculin reaction has not as yet been subjected to critical analysis in the light of investigations of the type detailed above. There are indications that there is a non-specific as well as a specific element in the behavior of tuberculin, not the least of which is Meirowsky's observation, confirmed by Zieler, that the sites of "syphilin" reactions react locally to tuberculin.<sup>7</sup>

The resemblances between the immunologic and allergic phenomena in syphilis and tuberculosis are strengthened by what is still inconclusive but highly suggestive evidence of the lapse in specificity of the Wassermann reaction when tuberculids or tuberculous allergic phenomena are concerned. The present clinical study and other observations on the behavior of the Wassermann reaction in glandular and occult tuberculosis are gradually accumulating a series of cases in which the presumption against syphilis is so strong that even a positive Wasser-

tion, the allergic response of a hypersensitized skin to emboli of tubercilli from a tuberculous focus elsewhere in the body.

2. Internists and general diagnosticians should find it worth while to familiarize themselves with the essential lesion of these type tuberculids, which may prove of great assistance in the recognition of obscure tuberculosis.

3. The tuberculid, when not ignored by the general diagnostician, is usually confused, as shown by this series, with acne and furunculosis with syphilis, especially if the Wassermann is positive, and on the whole with acute surgical conditions and ulcer varicosus. Therapeutic treatment for syphilis with arsphenamin are misleading in these cases. The diagnostic import of the lesions in obscure lymphadenitis was at times overlooked.

4. Association with tuberculosis in this series was evidenced by family history in one-fourth of the cases, incontestable objective signs in more than half (57 per cent), and presumptive signs of the disease in 70 per cent. One-third of the patients had radiographic signs of pulmonary tuberculosis; an equal number had suggestive or positive physical signs of lung involvement. The importance of lymphatic involvement is illustrated by the fact that two-thirds of them had a tuberculous lymphadenitis.

5. The type and location of the focus of tuberculosis do not seem to influence the tuberculid beyond the marked association with glandular involvement. On the other hand, the influence of vascular abnormalities and chronic passive congestion in the extremities is very apparent. Ninety-six per cent of the lesions involved the extremities. Lesions appeared on the ear in 13 per cent.

6. Slight fever at onset, loss of weight in 40 per cent, amenorrhea in 43 per cent of the women, moderate leukopenia, slight but occasionally severe anemia, and vernal periodicity are the significant signs. An onset and course marked by rheumatic symptoms is very common (46 per cent) and often misinterpreted. The recognition of the focus of tuberculosis must depend largely on objective evidence. There is a notable absence of cough, sweats, and hemoptysis. Florid, seemingly robust types of patients are not infrequently subjects of tuberculids.

7. Evidence of the importance of a septic focus and collateral types of infections appears from the history of tonsillitis in 39 per cent, "rheumatism" in 46 per cent, pneumonia in 26 per cent, grip in 54 per cent, and pleurisy in 18 per cent. These conditions seemed frequently to

stand in direct predisposing or exciting relation to the tuberculid. A total of 70 per cent had symptoms and findings suggesting the presence of a septic focus, and 62 per cent had had significant respiratory infections, excluding pleurisy.

8. While no direct relation of the tuberculid to the clinical condition of the tonsils could be established, 50 per cent of the patients had markedly septic tonsils, the remainder were passable, and none were normal.

9. Examination of the teeth by x-ray in a limited number of the later cases demonstrated the presence of septic foci in 45 per cent of nine patients. Other foci should be searched for.

10. While the secondary or septic focus was obviously present, its influence is obscure. Removal of the tonsils in seven cases failed to prevent the outbreak of a tuberculid or modify its course, and complete extirpation of all recognizable septic foci in two cases, without removing or treating the tuberculous focus, was also unavailing.

11. It is conceivable that the effect of a secondary septic focus, while not direct, is predisposing, in that toxins, or even bacteria, emanating from it may be in part responsible for the cutaneous allergy which is presupposed in explaining the pathogenesis of the papulonecrotic tuberculid. Evidences of the ability of a septic focus to produce or predispose to dermatitis, urticaria, and similar expressions of cutaneous hyperirritability, are accumulating. Further indirect evidence of a possible peculiar allergic state of patients with tuberculids is found in reported and personally observed cases of non-specificity in their Wassermann reactions, and in their hypersusceptibility to arsphenamin.

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mottled hands predisposes to the extent of more than 70 per cent the development of folliclis. It was a matter of note that all the patients who, at the onset of their cutaneous lesions, had been overweight showed the severest part of their manifestations in the lower extremities, a fact which accords well with the vascular stasis usually present in the legs. Obese persons, therefore, seem to be predisposed to the erythema induratum type of tuberculid, and the thin and neurotic, with marked vasomotor imbalance, to folliclis. Only 2 of 7 obese patients had folliclis and one of these was a child with a generalized tuberculid.

Summarizing the series as a whole from the standpoint of localization of lesions, more than half (57 per cent) of the patients had lesions on the upper extremities, but almost three-fourths (74 per cent) had them on the lower extremities, showing the distinct predilection for parts of slower circulation. Ninety-six per cent of the patients, or practically all, had lesions on either upper or lower extremities. Twenty-three per cent had lesions on the upper extremities and not on the lower, 43 per cent on the lower and not on the upper, so that the odds are 2 to 1 in favor of the lower extremity as a site of involvement. One-third had involvement of both extremities, one-third showed involvement of the trunk, and one-fifth of the face. It is of interest to note that 65 per cent of those in whom the face was involved had lesions of the ears, and that the ear was the seat of lesions in 13 per cent of the whole series.

The importance of the circulatory factor in the distribution of tuberculids is one of the strongest arguments for the bacillemic as opposed to the toxemic origin of the process. The presumption is that at points where the circulatory stream is moving most slowly the maximum opportunity for the deposit of organisms will present itself, and that lesions will tend to appear, as they do, in areas where one factor or another acts to delay the movement of the blood.

#### MISCELLANEOUS FINDINGS ON EXAMINATION

In the study of this series of cases a number of interesting miscellaneous findings developed. The recognition of concomitant tuberculosis in cases exhibiting a tuberculid is, on the whole, a matter of identifying signs by objective examination rather than of eliciting symptoms. Six of the patients had a temperature of 99° or over at the time of examination, although temperature is a much more important factor at onset, especially in those cases which begin as erythema multiforme.

*post hoc* thinking may be indulged in under such circumstances is fully appreciated, and for that reason what follows is to be interpreted as a preliminary report, albeit some attempt at critical analysis of the various factors in the treatment régime is made.

#### SUMMARY OF THE CLINICAL ASPECTS OF THE SERIES

For a fuller study of the clinical aspects of the group of tuberculids herein discussed, reference should be had to the previous studies. By way of summary it may be said that of the 20 treated patients, 6 presented the tuberculid known as folliclis, 1 had acnitis, which is the papulonecrotic tuberculid of the face, 8 had papulonecrotic tuberculids involving the trunk, 8 presented lesions of erythema induratum on the legs, 3 had tuberculous erythema nodosum in association with other tuberculids, and in 3 the condition was quiescent.

*Visceral lesions.*—Ten of the 20 patients (50 per cent) had demonstrable tuberculous lymphadenitis in situations that were at least in part accessible to local therapeutic measures, such as x-ray treatment and surgery. Of the remaining 10 patients, 8 were “occult” or obscure cases, exhibiting no recognizable physical signs, with the exception of one who showed evidence of tuberculous involvement of the right apex with a negative radiogram. Three patients had positive Wassermanns without adequate objective evidence of syphilis, a condition discussed in Study II of the series. Four of the 10 patients having tuberculous lymphadenitis showed suggestive or diagnostic radiographic signs of pulmonary tuberculosis.

All the patients belonged to a type of tuberculous subjects having a high native resistance to the infection. None of them was acutely febrile or rapidly progressive. Several were fat and florid and to all outward appearances in robust health, conforming thus to a type which is familiar in association with visceral tuberculosis. The remainder were of smaller stature and slighter build, exhibiting a moderate pallor with asthenia, and, with surprising frequency, arthralgias and myalgias of the type usually associated with pyogenic focal infection. Several of the patients had mild grades of anemia, with afternoon temperatures fluctuating between 99° and 99.6°. Cough, hemoptysis, and night-sweats were notably absent in the group as a whole. Loss of weight had occurred in a number of instances. In the overwhelming majority the cutaneous tuberculid was chronic, showing little disposition to remission and almost none to total disappearance. The group was,



therefore, a good one in which to employ new therapeutic methods since the presumption was strongly against spontaneous remission in the guise of therapeutic effects. A number of the patients have shown the characteristic tendency to spring exacerbation, and several of them have now been carried through one and even two such periods with remission.

#### SURGICAL TREATMENT OF THE TUBERCULOUS FOCUS IN ITS RELATION TO A TUBERCULID

The surgical work of the clinic has provided the opportunity for study, in connection with our work, the value of the surgical treatment of a tuberculous focus as a means of influencing a tuberculid. In estimating the effect of surgical extirpations of glands, however, it must be recalled that, as conventionally performed, such measures fall short of complete extirpation of the focus, and that results which such incomplete procedures fail to achieve can hardly be laid at the door of adequate surgery. On the other hand, the popularity of surgical treatment for axillary and cervical tuberculous adenitis justifies an estimate of the gross operative outlook when compared with a proposed medical procedure for accomplishing a similar purpose.

A survey of 100 cases of tuberculous glands undertaken as a preliminary indicated that 37 per cent of the patients had sustained one operation, 26 per cent had been operated on twice, and 37 per cent had been operated on more than twice. The highest number of operations sustained by any one patient was eight. The frequency of repetition noted must, of course, be ascribed, in part, to the impossibility or inadvisability, in certain cases, of attempting to extirpate a focus by a single procedure, and also, of course, to the inadequacy of the technique employed in some cases. None the less the figures are suggestive in the light of our findings in patients with tuberculids. Nine of a total of 30 patients had received operative treatment in the form of excisions of glands for tuberculous adenitis. Three had had one operation with relapse; 2 had had two operations with indeterminate results; 3 had had two operations with relapse, and 1 had had three operations and relapsed. Surgery had not, therefore, as applied in these cases, been conspicuously successful in eliminating the focus. In its relation to the tuberculid the following facts appeared:

The cutaneous outbreak had followed the operation in 4 cases—3 after the first operation and 1 after the second. Operation had no effect

whatever in 5 cases. In 1 of these one operation had failed; in the other 3 operations had been done without effect on the tuberculid. In 1 case constitutional benefit was reported but the tuberculid persisted.

While due allowance must be made for the smallness of this group of cases and for the unfairness of expecting one operation to accomplish what three may be necessary for, this much may be said to appear tentatively from our examination: Surgical treatment of a tuberculous focus as ordinarily carried out neither guarantees a patient against a subsequent tuberculid nor offers him any worth-while therapeutic prospect if one is already present.

It should be recalled, in considering this point, that the best available pathologic and experimental evidence points to the belief that a tuberculid means hematogenously distributed tubercle bacilli from an active focus. Its occurrence after operation is, therefore, evidence for clinician and surgeon alike, that operative effort to extirpate the focus has failed. The repeated failure of operation to cure the condition simply registers repeated failure to get at the active process. A number of patients with tuberculids do not exhibit gross foci susceptible of surgical treatment. Forty-four per cent of our patients showed no focus susceptible of surgical treatment. In such instances retroperitoneal and tracheobronchial tuberculosis, and signs suggestive of localized tuberculosis in the abdominal cavity, offer a plausible explanation, occasionally demonstrable at necropsy or by radiographic signs. It seems reasonable to believe that even in cases in which there is a grossly obvious focus such obscure and unreachable accessory foci may also exist. The failure of operation, when reasonably complete, to influence the course of a tuberculid should, therefore, it would seem, be interpreted as a signal to desist, and to adopt, in the place of further surgical intervention, measures to combat the focus constitutionally by increasing the patient's resistance and affecting the walling off of the focus by physiologic means. Only a long series of cases can demonstrate, of course, that the medical procedure should have been invoked in the first place, and the surgical procedure subordinated to it.

#### MISCELLANEOUS OBSERVATIONS ON TUBERCULIN TREATMENT, ETC.

The patients treated in this series offered opportunity for incidental observation of the effect or lack of effect of a miscellaneous variety of treatment. Of 5 patients with tuberculids treated with tuberculin, dosage and method of employment unknown, 2 reported themselves as

having been made much worse following violent reactions. One had observed no effect; in another the glands had subsided (cervical lymphadenitis) without affecting the tuberculid. A fifth reported herself improved. I myself have observed the tendency to marked and unfavorable reaction to tuberculin sometimes exhibited by this type of case, with rapid extension of the process, and believe that it may be aligned with the hypersensitiveness exhibited by cases of acute disseminating lupus erythematosus, in which reports of fatal outcomes are on record following the administration of small doses of tuberculin (Ravogli). MacKee has recently reported indifferent results in the treatment of a number of cases of the papulonecrotic tuberculid with tuberculin.

Three patients had received vaccines, 2 autogenous and 1 stock, presumably on a diagnosis of acne vulgaris or a pyogenic process. A patient with acnitis was made much worse, 2 others were improved, 1 of them a case of long standing. In an allergic complex, such as that which underlies the development of tuberculids, it is difficult to determine the rationale of such a procedure, though it is conceivable that the improvement may be due to an action on the secondary focus of pyogenic infection present in more than 50 per cent of these patients, as discussed in Study II. In both the patients who improved such foci were present; the one had very septic tonsils and the other alveolar abscesses. This aspect of the therapeusis of tuberculids, as well as their pathogenesis, deserves further study. The effect of a vaccine, like the probable effect of arsphenamin, may be that of a non-specific stimulation of immunity and of defensive processes, rather than a specific action upon the causal agent. One patient had received x-ray treatment to the lesions themselves. She reported that the ordinary dosages and methods were without effect, but that one "deep" treatment had been beneficial. The rationale of this procedure is also doubtful, in view of the pathology of the tuberculid. It is possible that the constitutional effect of intense x-ray treatment accounts for the observed improvement.

Arsenic in other forms than as arsphenamin had been administered to three patients. One had taken enough Fowler's solution to produce palmar keratoses and hyperpigmentation with little effect on the tuberculid. Another had received no benefit from the same preparation. One patient had received sodium cacodylate for anemia, with fair effect on the tuberculid. Her cutaneous lesions were subsequently cleared up by arsphenamin.

Mercury was intensively administered to five patients on the finding of a positive Wassermann. Three of them showed a normal tolerance of the drug by inunction or injection. The other two were less favorably affected. One of them was improved by iodids. Four of them noted improvement under arsphenamin. One patient had received iron for the anemia which marked the onset of active glandular tuberculosis, with marked benefit.

Local measures used in the cases observed were of little avail. A surprising amount of meddlesome surgery had been done on some of the lesions, notably when occurring on the leg, even to the point of repeated total excisions of lesions and deep incisions for supposed osteomyelitis which had so damaged the blood supply of the tissues that satisfactory results could not subsequently be obtained.

*Arsphenamin and arsenical synthetics in the treatment of tuberculids.*—The employment of arsenic in a variety of forms in the therapy of cutaneous tuberculosis has, of course, been familiar practice for a number of years. On the other hand, little of conspicuous benefit has been reported from it except perhaps in the sarcoids, a group of supposed tuberculids still of unsettled pathogenesis. With the advent of a new and highly potent arsenical in the form of salvarsan, an immediate attempt was made to apply it to the therapy of cutaneous tuberculosis. Herxheimer and Altmann, for example, early reported favorable results from its employment, and asserted that they observed local reactions from its use similar to those obtained by tuberculin. While this latter observation has not been generally confirmed, other favorable therapeutic reports appeared. Just before the war Ravaut, followed by Tzanck and Pelbois, published accounts of marked benefit to a number of types of lesions of tuberculous origin from courses of salvarsan averaging three to six injections in number. The latter authors also urged the importance of an appropriate hygiene in the management of these cases. Sequeira noted the improvement of lupus vulgaris under atoxyl and salvarsan, after mercury and the iodids previously administered had failed. The effect of arsphenamin on tuberculous subjects had been experimentally studied by Nicolas, Courmont, and Gaté in 1912, and by Courmont and Durand in 1913. These authors found that in experimental animals a marked increase in agglutinins for tubercle bacilli occurred in the blood on the administration of arsphenamin. Nicolas, Courmont and Charlet found a similar phenomenon to occur in the blood of tuberculous patients, and established at the same time that

the increase occurs in those in whom the agglutinins are already high or on the increase rather than in those in whom they are low. In the therapeutic series of pulmonary cases in which novarsenobenzol (Bilek) was given in small doses per rectum at frequent intervals, these authors felt their impression, based on experiment, to be confirmed. They concluded that the drug should not be used in progressive or grave cases which are aggravated by it, but in discrete limited involvements, having a tendency to favorable course. The action was compared to that of sodium arsenite, and arsphenamin rated as a reinforcement in selected cases. Potter, in summarizing his experience with 21 cases of combined tuberculosis and syphilis, reports favorably on the effect of arsphenamin, but cautions against its use in active, acute, and miliary cases. He also noted the occurrence of tuberculin-like focal reactions.

My own experience with arsphenamin, as represented by the type of tuberculous involvement included in the present series of cases, is in accord with that of the authors mentioned. The effect of the drug does not suggest that of a specific bactericidal agent, but rather that of a fortifier of individual resistance and a means of stimulating the defensive mechanism of the body against the tubercle bacillus. (Clinical study does not, of course, establish whether this is accomplished by the increased formation of specific agglutinins, as suggested by the work of Nicolas and his collaborators, or by a less specific modification of the allergic and metabolic balance of the patient. My own observations in the use of arsphenamin in double infections with tuberculosis and syphilis accords with that of Potter in opposing the use of the drug in acute or unfavorably progressing cases or in those showing evidence of low resistance. One of the two conspicuous failures in our tuberculous therapeutic series was likewise a case of low resistance, running a rapidly progressive course. The patient died eight months after she was first seen. The ideal type for the use of arsphenamin, so far as our observations thus far suggest, is the patient who, while perhaps not on the up grade, is at least holding his own, who has seasonal periods when his resistance for the time being suppresses or controls all manifestations of the infection, and who rallies from the exacerbations produced by intercurrent ailments without a permanent break in his recuperative powers. The effect of arsphenamin in hastening the healing of ulcerative tuberculids, while not so striking as that in syphilomas, is, none the less, marked enough to suggest a degree of special action by this drug on granulomatous tissue, comparable to that exerted by potassium

iodid, for example. This type of effect may be similar to the effect of arsphenamin on blastomycosis, and, in my own experience, to the effect on occasional cases of sporotrichosis.

#### THE ARSPHENAMIN COMBINED TREATMENT OF TUBERCULIDS

The use of this somewhat bizarre phrase is intended to imply that the régime actually employed at the present time on the service of the Section of Dermatology in the Mayo Clinic is a combination of several therapeutic methods, including: (1) The intravenous administration of arsphenamin or neoarsphenamin; (2) the x-ray to detectable and accessible foci of glandular tuberculosis; (3) an antituberculous outdoor régime; (4) a forced diet; (5) the removal of secondary foci of pyogenic infection in tonsils, teeth, or elsewhere, and (6) the correction of vascular stasis and vasomotor abnormalities involving the extremities. Two items usually emphasized in texts we have found to be of secondary importance; that is, rest and local treatment of the lesions. It has been our experience that the former, while of value, need not be carried to the point of rest in bed with elevation of the affected leg.

*The arsphenamin treatment of tuberculids.*—Our preference in the selection of the preparation of arsphenamin is for arsenobenzol Polyclinic (Schamberg), although we have occasionally employed novarsenobenzol (Billon). The rather marked tendency to reaction exhibited by the patients has led us to prefer the former because of its exceedingly low toxicity, and because of the same tendency to a lower intrinsic toxicity of the dihydrochlorate as compared with the monomethylene sulphonylate of sodium salt which is observed in syphilis. The drug is given in courses, with a view to taking advantage of its cumulative effect. The average course is six injections, though later courses may be shortened. The dosage must draw a compromise between a maximum introduction of arsenic and the avoidance of toxic and debilitating effects from overdosage. The initial dose should not exceed 3 decigrams; the average dose, 4 to 5 decigrams of arsphenamin or its neoarsphenamin equivalent. The injections should be given at weekly intervals. For the first two or three patients of our series, and for one seen subsequently but treated elsewhere, the dosage was small and the treatment desultory and irregular, to which we ascribe much of the relatively unsatisfactory results. The method should not be adjudged inefficient or inapplicable to a particular case until it has had systematic and persevering application.

At this stage in our employment of arsphenamin I feel it important

to emphasize the repetition of the course as a seasonal reinforcement of the patient in the months of the year in which the tendency to relapse is usually greatest, that is, in March and November. In our series of 17 active cases, 4 patients received short courses of 4 or 5 injections each; 6 have received thus far one course of 6 injections each; 3 have received initial courses of 8 injections. Three received two courses, totaling from 8 to 10 injections. Two received three courses, totaling 10 and 11 injections, respectively. One patient has received five courses, totaling 24 injections. The improvement exhibited by a given case is only incidentally a function of the number of courses. By estimating the total dosage in terms of grams of arsphenamin there is apparent, however, a relation between the total dose and the degree of improvement. Of 11 cases in which the improvement was rated as 4 on a scale of 0, 1, 2, 3, 4, the average dose was 3.8 gm. This omits from consideration one of our most remarkable cases, which was transformed by a total dosage of 10.8 gm., too high to be fairly compared with the other five. Of the remaining cases, in which the patients showed improvements ranging from 0 to 3 and averaging 2 plus on the same scale, the average total dosage was 2.6 gm., or 1.2 gm. less than the dosage of the 4 class.

Improvement under treatment must be considered under three heads: First, improvement in the cutaneous lesions of the tuberculid; second, improvement in the constitutional condition of the patient; and third, improvement in the tuberculous focus if observation of it is possible.

The improvement effected in the tuberculid by the administration of arsphenamin is often the first change apparent under treatment. Usually with the first and second injections, but sometimes not until the fourth, there are marked drying and reduction in the size of any active lesions present, and a diminution in tenderness. The course of any new lesions which may appear is markedly shortened, and the number of recurrences greatly decreased. In a case which is progressing favorably new lesions have ceased to form by the end of the first course, although even in cases which ultimately remain clear there may be slight relapses. In several of the cases in our series which were at first rated as failures the patients have recently reported that they consider themselves much improved, owing to the fact that although lesions still appear, they have practically ceased to be troublesome.

The treatment results in our series may be summarized from the standpoint of cutaneous lesions as follows: Of 17 patients presenting active lesions, 9 (53 per cent) have been completely cleared of active

lesions—5 in the first course, 3 in the second, and 1 later. Four patients have been improved, though not protected from relapse; treatment of these is incomplete. Four cases of the series (24 per cent) were rated as failures before the sending out of a questionnaire while the present study was in preparation. As a result of this questionnaire it appears that one of the “failures” rates herself as 50 per cent better than before treatment. She still has nodular recurrences, but no ulcers. Her total dosage was 4.1 gm. in 10 injections. The second “failure” reports herself as “a great deal better,” and as having gained 40 pounds in weight, although she is again down to medium weight. This was one of our early patients who received unsystematic treatment with rest in bed. The outlook for complete symptomatic recovery was greatly reduced by the amount of surgical trauma inflicted on the legs, which were the sites of most of the lesions. Numerous incisions, excisions, and attempts at plastic treatment of the ulcers had practically ringed the affected area about with scar-tissue, creating an artificial stasis. The two bona fide failures were a woman with an erythema induratum of the calf of one leg and a tuberculosis verrucosa cutis of the other, with a progressive anemia and asthenia. While no active focus could be identified, in response to a questionnaire she was reported dead. The second failure was in a rather obese woman, a low resistance type, with innumerable scars of suppurating cervical glands and a history suggestive of tuberculous peritonitis with a focus in the adnexa. She had an inadequate early course, with overattention to local measures, and relapsed the following spring, with more suppurating glands. If in 2 of the 4 cases described the patients may be rated on their own estimate as improved, the percentage of total failure to improve the cutaneous condition will be reduced to about 12 per cent.

Precisely how much of the constitutional improvement manifested in these patients is to be attributed to the arsphenamin which they receive it is difficult to say. Undoubtedly the storage of arsenic in the liver and spleen which occurs during a course of injections provides the basis for a prolonged tonic effect. On the other hand, a number of our patients showed definite improvement in their general symptoms while receiving the first course of injections, and this in the face of the fact that they were not encouraged to adopt any special hygienic measure until the interim between courses, and again in spite of the fact that some of them resumed hard work which they had been physically unequal to prior to beginning their course of injections.



Gain in weight and an improvement in or complete disappearance of "rheumatic" symptoms, if present, were the two most immediate and conspicuous effects on the general health of the patients. The weight gains during the course of treatment varied from 1.5 to 15 pounds. The tendency to gain weight continues to manifest itself after the completion of the course, and in fact many of the most striking increases occurred in the month following the arsphenamin treatment—a phenomenon we have repeatedly observed in the treatment of syphilis. While the weight changes are undoubtedly to some extent influenced by forced diet and hygiene, the changes occurring under arsphenamin alone are sufficiently marked to make it probable that the drug was largely instrumental in the improvement.

Of 14 patients on whom definite data are available, not one has failed to register some gain in weight. Seven (50 per cent) have made gains varying from 7.5 to 40 pounds, in periods varying from two to twenty-four months. Four patients gained more than 20 pounds. While the peak of the weight curve is not always maintained, 4 have held gains of 15 pounds or more for from one to two years.

Loss of weight may occur, especially in the obese. Three patients lost from 7 to 10 pounds during their course of arsphenamin injection. This was accompanied by an increased sense of well-being rather than the reverse.

The effect of arsphenamin on the arthralgias and vague aching pains which many of these patients present is often very striking. A patient who had been operated on for a tenosynovitis without improvement and who had multiple swollen and painful joints (both ankles and the right knee), was completely relieved of her symptoms by the fourth injection of her first course and has suffered no recurrence. Another, at one time bedridden for weeks with "rheumatism," has had no such symptoms since her first course, and only notices a slight aching when extremely fatigued. A barber who registered the maximum weight gain under treatment remarked enthusiastically that he had gone back to earning a living after having been unable to be on his feet for more than an hour a day for two years on account of pain and swelling of the ankles.

While our observations are still too few in number to permit of generalizations, we have not been impressed with any marked influence of the arsphenamin on the tuberculous adenitis in so far as it can be judged by a reduction in the size of the glands. In two cases actual

increase in the size of the glands seemed to occur during the early part of the course, and a rapid reduction subsequently followed the first one or two Coolidge tube exposures. In other cases the glands were very little influenced. Several patients, in response to a questionnaire, report reductions in the size of the palpable glands, but such reductions occur so often as a result of improved hygiene and a period of freedom from secondary infections that no conclusions can be drawn.

About 50 per cent of patients with tuberculids seem to exhibit a distinct idiosyncrasy for arsphenamin, a figure very much in excess of the average reactivity displayed by syphilitics for a similar dosage and interval scale. Of 9 patients, 4 had single or repeated nitritoid crises, 4 had pronounced gastro-intestinal reactions, and 1 developed a toxic erythema, a very rare accident on our service. As in the treatment of syphilis, a definite overtreatment syndrome, with marked idiosyncrasy, loss of weight, pallor, and nervousness, is an indication for abandoning arsphenamin.

*X-ray treatment.*—Our experience with the x-ray in the treatment of tuberculids has been largely confined to its use in treating a glandular focus. The earlier technic employed was less efficient than the later, and for that reason no final conclusions are possible. The treatment recently given under the direction of Dr. Jones in the Department of Radiology of the Mayo Clinic has consisted of a four-and-one-half-minute exposure with the Coolidge tube on a 4-inch square surface over various parts of the mass, using a current of 5 milliamperes with a 7- to 9-inch spark-gap and a focal skin distance of 9 inches. The filter employed has consisted of 3 mm. of aluminum, 1 cm. of wood, and 5 mm. of sole leather. With this technic we have seen a definite effect on glands which we did not believe could be attributed to any other factor in the treatment.

On the other hand, the effect of x-ray treatment of the glands on the tuberculid seems to us more open to question, especially when compared with that of arsphenamin. One patient who improved slightly under x-ray alone registered the most surprising gains under arsphenamin at a considerably later period, when the ray had been discontinued and its effects must have worn off. A second patient received x-ray to the glands at intervals without effect on the tuberculid or the glands, but the tuberculid improved subsequently under arsphenamin. In a third patient the lesions were cleared up by arsphenamin and no x-ray was employed until later. Three of six patients presenting a glandular focus

made remarkable gains without any x-ray, and in several occult cases in which the patient presented no indication for its use remarkable improvements were likewise made. While x-ray treatment of the focus of tuberculous infection in a glandular case has its function, it cannot be regarded either as a substitute for arsphenamin in the control of the tuberculid or as comparing with it for promptness and efficiency in the cases under our observation.

*Outdoor régime, forced diet, and rest.*—Since it is axiomatic that the treatment of a tuberculid is that of the underlying tuberculosis, emphasis



Fig. 239.—Acanthosis, the papulonecrotic tuberculid of the face. Scar of operation for tuberculous adenitis visible on the neck. The eruption followed the operation. Photograph taken before arsphenamin treatment was begun.

has been placed with the patient on these means of cultivating an increased resistance. That their part is to increase the permanence rather than the striking quality of a therapeutic result is the impression derived from observation of those of our series who have adopted our recommendations. A number of patients have made and held marked improvements without giving this aspect of their treatment the attention it deserves. On the other hand, the four or five patients who have been longest under observation and give the greatest promise of per-

manence have at least slept outdoors, even though following indoor occupations, and have conformed to the general principles of antituberculosis hygiene. Rest, particularly in bed, has not been urged on our patients at any stage, and we have noted distinctly inferior results in our earlier cases when the patients were confined in order to secure the effect of rest on the lesions. Several patients have had notable results while pursuing strenuous occupations, such as housework sixteen hours a day, barbering, and heavy teaming.

*Treatment of the secondary focus of pyogenic infection.*—As shown in

y II, a high percentage of patients exhibiting cutaneous tuberculids with a secondary focus of pyogenic infection in the form of septic abscesses, alveolar abscesses, and possibly, in some cases, foci such as infected gallbladders, etc. Where such a focus could be identified, we have found it advisable to remove it, although its precise rôle in the production of the tuberculid is undetermined. Such a removal is not sufficient in itself to cause the disappearance of a tuberculid without appropriate general measures and special treatment directed at the tuberculous focus if it can be identified. We observed in one case, however, that a single obstinate and persistent lesion on the leg which had refused to yield to the régime which had cleared up all the others, healed after the removal of markedly septic tonsils. On the other hand, in several of our patients the tuberculid appeared at varying intervals following tonsillectomy.

#### *Correction of vascular stasis.*

*The value of the elastic bandage in hastening the involution of papulonecrotic lesions on the legs, even in the absence of gross vascular abnormalities, such as varicose veins, was early apparent, and did much to keep our patients out-of-doors and active.* In cases exhibiting vasomotor anomalies, as in the thinner and more neurotic types of patients, two pairs of stockings, silk and wool, or specially warm clothing and gloves, were of value in improving the peripheral circulation and diminishing the severity of recurrences.

*Miscellaneous general observations.*—Taken as a group, the least favorable results are to be expected from the obese, florid types of patients. The majority of them have erythema induratum, and the marked stasis element in the blood supply to the leg seems to predispose them to recurrence, although the temporary therapeutic response of a



Fig. 240.—After five injections of arsphenamin—only scars and pigment macules remain.

group of lesions may be good. Seventy-two per cent of the patients having an occult or obscure focus of tuberculosis were in the less successful group as regards therapeutic results, while only 28 per cent of patients of this type make a maximum improvement. When anemia is a prominent feature, the internal administration of iron is necessary to secure a marked rise in hemoglobin, the arsphenamin having proved less efficient in this regard.

#### CASE HISTORIES ILLUSTRATING THE TREATMENT DESCRIBED

**CASE 1 (161592).**—A girl, aged nineteen years, had been the victim of severe and extensive papulonecrotic lesions with erythema induratum



Fig. 241.—Four months later, after three more injections of arsphenamin. Complexion clear and blooming.

since the age of nine, associated with a severe tuberculous adenitis and with tuberculous keratitis and severe anemia. Under 24 injections of arsphenamin, totaling 10.8 gm., the patient has gained 28 pounds in weight and held it, and is practically free of lesions. She has pursued exacting indoor occupation for one and one-half years and is in excellent general health. She has had one abortive attack of episcleritis since being under observation, but has shown no other manifestations of tuberculosis. Period of observation, two years.

**CASE 2 (174923).**—A girl, aged twenty-four years, unsuccessfully operated on for tuberculous glands, has had a long history of severe papulonecrotic lesions on the buttocks, thighs, and legs, and arthritic and myalgic symptoms of such severity as to confine her to bed for weeks at a time. Under 16 injections of arsphenamin, totaling 6.0 gm., combined with an outdoor régime and nine Coolidge tube exposures, she has gained 20 pounds in weight, maintained it for twenty-two months, has never had a lesion since the first course, and now does general housework at home, whereas before treatment she was a semi-invalid.

**CASE 3 (200833).**—A nurse, aged thirty years, who had been operated on twice for tuberculous cervical adenitis with only partial success, had

a profuse acnitis of the face and ears and a papulonecrotic tuberculid of the forearms. She had received vaccines for acne, which made her worse. The eruption vanished before the completion of a five-injection course, and at the end of a second additional course of three injections, with a total dosage of 2.6 gm., her complexion was blooming. Her reply to a recent questionnaire states that she has followed only a partial outdoor régime, has gained 7.5 pounds, of which she has held 3 pounds, feels well, has never had a relapse, the glands are palpable and about stationary, and she is contemplating Red Cross work (Figs. 239 to 241).

**CASE 4 (212370).**—A girl, aged twenty-five years, had been seen by numerous internists and surgeons without a diagnosis having been made.



Fig. 242.—Lesions of folliclis before the administration of arsphenamin.

She presented a typical folliclis, with an erythema induratum and papulonecrotic tuberculid. In addition she had a tenosynovitis which had been unsuccessfully operated on and a slight hydrarthrosis of both the ankle and the right knee, with marked arthralgia and myalgic pains. A tonsillectomy and appendectomy previously performed had been without effect on the trouble. Ten injections of arsphenamin with an outdoor régime between the two courses resulted in a net gain of 14 pounds in weight, and the total disappearance of all symptoms and signs, including the eruption, the tenosynovitis, and the hydrarthrosis by the end of the second course. The patient has been under observation for ten months (Figs. 242 and 243).

**CASE 5 (226884).**—A man, aged forty-two years, a barber, who had been unable to work for two years, had an extensive papulonecrotic tu-

berculid of the legs and trunk with enlarged cervical glands. Under a course of eight injections of arsphenamin, totaling 3.4 gm., he gained 13.5 pounds in weight, returned to full-time work, and has followed special hygiene. He has subsequently gained an additional 7 pounds. X-ray treatment was not begun until the end of the course, so that the effect must be attributed entirely to the arsphenamin. All cutaneous lesions have disappeared. The glands, while smaller, are still present.

CASE 6 (218528).—An anemic but well-nourished woman of twenty-six years who had lost 40 pounds in weight in four years, presented a papulonecrotic tuberculid of the leg of eighteen months' duration, with erythema induratum and a mild secondary anemia without obvious



Fig. 243.—Same case as Fig. 242. Lesions healed following six intravenous injections of arsphenamin. No other treatment used.

signs of tuberculosis. Under a single course of six injections, totaling 2.4 gm. of arsphenamin, she reports, after nine months, a gain of 17 pounds in weight and the "wonderful" disappearance of her lesions without signs of recurrence.

CASE 7 (197425).—A girl, aged twenty-one years, of the overweight, florid, and blooming type, presented the ulcerative lesions of erythema induratum on both legs, with numerous nodules. She received 10 injections of arsphenamin, with a total dosage of 4.1 gm., doing heavy housework sixteen hours a day during the treatment, without any special hygiene other than the use of elastic bandages. All the ulcerative lesions disappeared, but nodules occasionally recurred. At the end of fourteen months, in reply to a questionnaire, she reports an

improvement of 50 per cent. The lesions are smaller, fewer, and less painful than before treatment and last only about a week. She is doing indoor work and sleeps out-of-doors.

It will be apparent, from the discussion and the cases cited, that final judgment cannot at this time be passed on the use of arsphenamin, either alone or in conjunction with other measures in the management of tuberculids of the papulonecrotic and erythema induratum types. Only time can establish the permanence of the results. On the other hand, there seems good reason to believe that it has a marked beneficial effect, proportional to some extent to the persistence with which it is used and to the total dosage of arsphenamin administered. Some of the results produced in the patients longest under observation and treatment have been really remarkable, and failure and lack of improvement can, in a number of instances, be explained by desultory methods. In general, the obese types of patients, and those with occult tuberculosis, offer less outlook for radical improvement than other types, but it is impossible at the present time to generalize or to predict in which case improvement may or may not be expected. When the long duration and the persistence of tuberculids of this type and the heretofore rather dubious results of conventional methods are taken into consideration, I believe the intensive use of arsphenamin, in conjunction with a régime which treats the underlying cause as well as the symptom, deserves to be better known and more extensively employed.

#### SUMMARY

1. This study deals with a group of 20 cases of various types of papulonecrotic tuberculid and erythema induratum in which arsphenamin (Ehrlich "606") was used with good effect, in combination with a systemic régime and x-ray treatment.
2. Over half the cases thus treated had demonstrable tuberculosis, usually in the form of a lymphadenitis.
3. Surgical treatment of the lymphadenitis in nine cases had not demonstrably affected the tuberculid.
4. It would seem, from our series, that the appearance or the persistence of a cutaneous tuberculid following reasonably complete surgery is an indication for a discontinuance of surgical treatment of the tuberculous focus, and the adoption of a medical means of fortifying the patient against the progress or recurrence of his tuberculous infection.



5. The intravenous administration of arsphenamin would seem to afford such a medical means of fortifying the patient's resistance to tuberculosis when combined with an antituberculous hygiene and x-ray.

6. Arsphenamin offers an excellent means of treating selected cases of obscure tuberculosis, as evidenced by the presence of a tubercle and the absence of a demonstrable focus. Its use in febrile, acute, or rapidly progressive cases is not advised.

7. Arsphenamin alone is apparently able to produce a striking effect on cutaneous tuberculids. Fifty-three per cent of 17 cases have been completely cleared of lesions, and only 12 per cent have failed to secure a definite improvement.

8. Arsphenamin is also apparently instrumental in producing marked constitutional improvement in these cases, evidenced especially by a gain in weight and the disappearance of the "rheumatic" symptoms complained of. Gains of from 1.5 to 40 pounds were registered in our series.

9. The effect of arsphenamin upon the tuberculous adenitis, when present, is indeterminate, but probably not striking.

10. X-ray treatment assists in the reduction of the glands, but we have not found it to compare with arsphenamin in its influence on the general condition or on the cutaneous tuberculid.

11. An outdoor life, forced diet, correction of vascular abnormalities and stasis by elastic support, and careful extirpation of secondary foci of pyogenic infection in tonsils, teeth, etc., are subsidiary but important elements in successful treatment.

12. These observations are offered as tentative and preliminary, although several of our cases are completing their second year of freedom from lesions and striking general improvement.

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## SKIN-GRAFTING\*

J. C. MASSON

At no time in the world's history have there been under treatment many persons injured and crippled as now. As a great majority of these are suffering from infected wounds, frequently with a great deal of sloughing and destruction of extensive areas of skin and superficial tissues, anything that will tend to hasten healing and cover raw surfaces will be a great benefit to the patient, and a great saving in time and money.

Much has been done in the way of simplifying dressings, and in the control of infection by the scientific application of time-honored surgical principles, and the introduction of antiseptics that have a maximum bactericidal action and a minimum destructive action on the tissues. I shall not, however, dwell on the treatment of wounds or on the major surgical operations indicated, but shall confine myself to the final stage of the treatment of most infected wounds, that is, the covering of the raw surfaces with skin.

A great many wounds primarily infected are, under modern methods, made rapidly sterile, as shown by the disappearance of pus and bacteria and may then be closed with impunity like any fresh wound. But in many of these cases, when there has been extensive destruction of skin, the healthy edges of the raw surfaces cannot be brought together by the ordinary plastic method, and skin grafting must be resorted to.

In reviewing the history of surgery it is not surprising to note that skin grafting was one of the first operations attempted; in fact, it is asserted that the ancient Hindus and Egyptians successfully transplanted skin, before the Christian era and it is generally accepted that this operation has been done with varying degrees of success in different parts of the world ever since. It was not, however, until 1869, following the reading of a paper and the presentation of a case by Reverdin before

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the Société de chirurgie in Paris, that it was accepted as a regular surgical procedure, and since that time a great deal has been written on the subject.

The grafts, as first suggested by Reverdin, were very similar to those that we now accept as probably of the best type of graft for use in the ordinary case in which closure of the wound is the all-important consideration. These are small island grafts, principally epidermic, but containing some dermis in the center, and called by Davis small deep skin grafts. The other accepted and useful grafts are known as Thiersch grafts and Wolfe grafts. The former are thin sheets of skin, removed with a razor, and include all the layers of the epidermis and possibly a portion of the dermis; the latter are composed of the entire thickness of the skin, and when successfully used are the most satisfactory.

Skin-grafting is divided into three distinct types, depending entirely on where the grafts are obtained: (1) Autoplastic grafts—skin taken from another part of the body of the patient; (2) isoplastic grafts—skin taken from another person, and (3) zoöplastic grafts—skin taken from one of the lower animals. All authorities agree that the autograft is the most satisfactory, and a great many hesitate to use even isografts when it is possible to get skin from the patient.

I myself have had no experience in the use of zoödermic grafts, but am satisfied that there is a much larger field of usefulness for the isograft than is generally believed. When one takes into consideration the ease with which good grafting material may be obtained in the operating room without discomfort or inconvenience to the donor, and with the removal of all dread of the operation from the recipient, one is convinced that it should certainly be more frequently practised. In isografting the cause of failure should not always be attributed to the graft itself, since it may be due to the patient, to the condition of the wound, or to the after-care and dressing, etc. This problem is especially difficult to solve in private practice, in which time is such an important consideration to the patient and little or no help can be obtained by experimental work.

In all the patients requiring skin-grafting who were under my care during the past year the blood of the donor, as well as that of the recipient, has been tested for agglutination. The results have been very interesting and instructive, and I feel sure will add a great deal to the popularity of the use of the isograft. In many cases the method will obviate the unnecessary removal of skin when there is little or no likeli-

hood of its taking. I have tested the principle with the three varieties of grafts, and am satisfied that blood grouping is just as important for good results in skin-grafting as it is necessary in transfusion, and that it is governed by the same principles.<sup>2</sup> While the results obtained are not positive, nevertheless I have never had the skin take which was removed from a donor whose red blood-corpuscles were agglutinated by the serum of the patient. The results in all other cases have been very satisfactory, almost, if not entirely, equal to autodermic grafting.

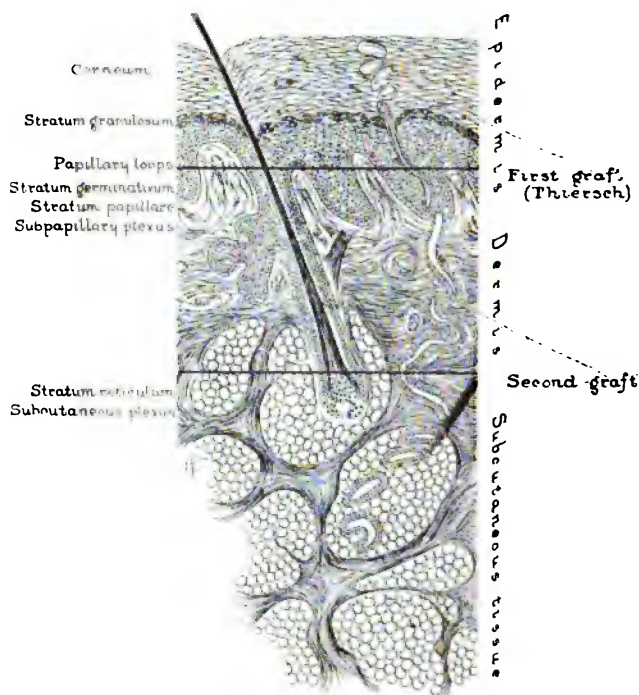


Fig. 244.—Normal skin, showing part utilized in Thiersch graft, and the deep part utilized by a new method.

most cases in which a donor's skin is to be used a Wassermann test should be made to guard against syphilitic infection.

In any case in which it is considered expedient to resort to skin-grafting the first consideration is to have the raw surface in a healthy condition. Experience shows that only poor results can be expected on an indolent ulcer, one covered with exuberant granulation tissue or one in which the microscopic slide shows numerous bacteria. Grafting may be satisfactorily done on fresh raw surfaces, but pedicle or plastic grafts

as a rule, more satisfactory in these cases, and true skin-grafting is more frequently indicated as a secondary method in closing open wounds or ulcers.

In all chronic ulcers, especially those resulting from x-ray or electric burns, the first consideration is to improve the circulation in the wound and to stimulate healing by the removal of the unhealthy granulations, either by curetting or by excision of the ulcer. Grafts may be applied immediately, but in most cases it is advisable to apply to the surface hot saline or boric dressings until it is covered with healthy granulations, and in some cases it is desirable to use a salicylic acid ointment (8 per cent) once in two days until a healthy condition of the granulating surface is obtained and a thin pellicle of new skin begins to form along the edge. Satisfactory results can then be expected from skin-grafting.

In the more recent cases, such as are so often seen in patients following burns, extensive superficial infections, or radical operations in malignancy, the best plan is to apply hot saline, neutral solution of chlorinated soda (Dakin's solution)

or dichloramin-T, until the wound is made sterile, as shown by smears on three consecutive days. The grafts may then be applied direct, or, if the granulations are exuberant, they may first be curetted away or rubbed off with a piece of dry gauze, controlling hemorrhage by pressure with gauze wrung dry from hot saline solution and applying the grafts immediately, pressing them well into place with moist gauze. If there is much oozing, it is better to delay the placing of grafts for twenty-four hours, keeping up the hot moist dressings.



Fig. 245.—Ordinary method of obtaining Thiersch graft.

The types of grafts to be used and where they shall be obtained are very important considerations. The full thickness, or Wolfe graft, gives the most normal looking and best functioning skin, but has the disadvantage that it is not so apt to take, as is either the Reverdin or Thiersch graft. However, in annular ulcers of the extremities, around joints, or in dealing with extensive areas, it is necessary to have at least a part of the surface covered with grafts of the entire thickness of the skin.

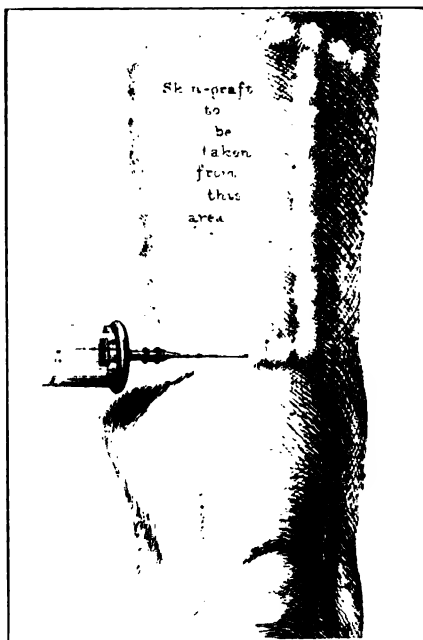


Fig. 246.—Superficial blocking with local anesthesia for skin-grafting.

In deciding where to obtain grafts, the type of skin desired should naturally be considered. For most cases the skin from the anterior and outer surface of the thigh or upper arm will be found best, whether it be from the patient himself or from a donor.

General anesthesia is frequently advisable, but even extensive grafts may be obtained under local anesthesia with very little discomfort to the donor, although so far as the operation or the surgeon is concerned, the latter has no advantage. It is much easier, however, to obtain a donor if it is understood that he will not be anesthetized.

It makes very little difference what method is used in preparing

the skin, and the iodine method is as satisfactory as any. The area is first cleaned with benzine containing 1:1000 iodine, and after drying, it is given two coats of 3.5 per cent iodine in alcohol. Figure 244 is a transverse section of the normal skin. A Thiersch graft is then cut after the ordinary method (Fig. 245). If local anesthesia is to be used, the skin is injected, as shown in Figure 246. If the skin is thick, a second layer may be removed from the same area in the same way, or small island grafts may be taken from the center of the raw surface to include some of the deeper layers of the epidermis and some of the superficial layers of the dermis (Fig. 247).

advisable to reduce the size of the wound, especially if much of the has been removed, by cutting an elliptic piece of tissue (Fig. 248) turning the edges together with silkworm gut and horsehair. The thus removed may also be utilized for grafting by cutting it into sectional grafts (a term used by Douglas, Colebrook and Fleming) applying just as the Reverdin grafts are applied. Figure 249 shows

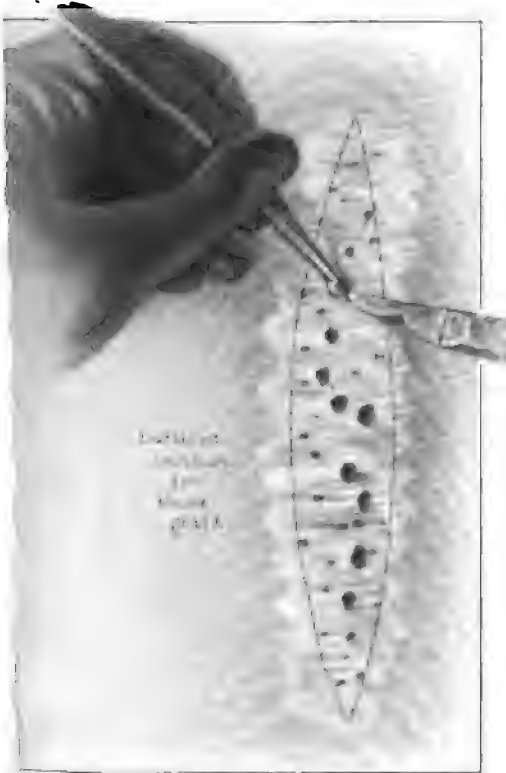


Fig. 247.—Further utilization of area from which Thiersch graft has been removed.



Fig. 248.—Excision of remaining layers of skin from surface denuded by Thiersch graft.

the wound covered with Thiersch grafts and small, deep grafts taken from the denuded area. The advantages of this method are: (1) Grafting material equal to twice the denuded area is obtained; (2) it is easily and quickly done and is especially suited for local anesthesia, and (3) the clean-cut wound may be expected to heal by primary union after being sutured with silkworm gut and horsehair, which has a distinct



advantage over the raw area left after the Thiersch method or the necessary multiple wounds of the Reverdin method.

If large grafts, either Thiersch or those from superficial dermic layers are used, they should be punctured at numerous points to allow the escape of serum, which would otherwise tend to float them from surface.

The type of dressing to use is of the utmost importance, and varies with the nature of the case. If the wound is completely covered with Thiersch grafts, the open method of treatment, that of protecting the surface with a wire screen, is probably the best, with an occasional removal of any crusts or thick secretions and the application by atomizer of dichloramin-T (4 per cent) or neutral solution of chlorinated soda.

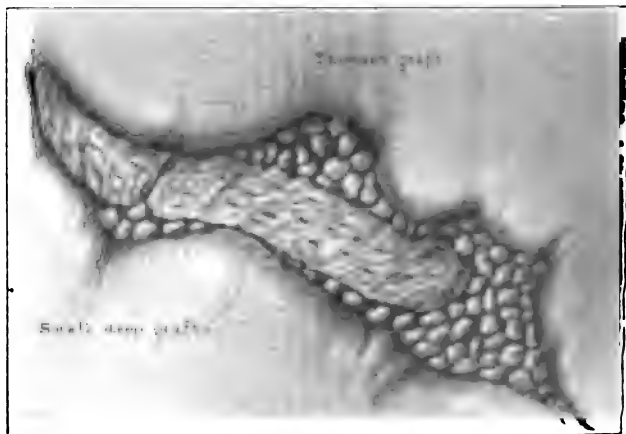


Fig. 249.—Wound covered with Thiersch grafts and small deep grafts taken from denuded area.

If the wound is only partially covered with grafts, the most satisfactory dressing is first to cover the raw surface and grafts with open-mesh net that has been previously impregnated with paraffin, and then to apply a wet dressing, which should be changed every four hours for three days without disturbing the paraffined net, the latter being held in place by sutures or by applying soft paraffin along the edges to fix it to the surrounding skin. Open-air treatment is then combined with hot dressings, the hot dressings being used at night and the wound left exposed during the greater part of the day and sprayed once or twice during the twelve hours with neutral solution of chlorinated soda. As a rule, grafts have taken well in one week's time, after which sterile petrolatum makes a very satisfactory dressing.

requently the paraffined net becomes firmly adherent to the grafts : wet dressings are being combined with open-air treatment; but may easily be freed by applying a liberal petrolatum dressing or by rubbing with liquid petrolatum for from four to six hours before attempting its removal.

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## A REVIEW OF THE ROENTGENOLOGY OF SYPHILIS\*

R. D. CARMAN

Osler, in the 1917 edition of his text-book on the "Principles and Practice of Medicine," does not mention the use and application of the roentgen ray in the diagnosis of syphilitic lesions and manifestations, although in view of the accumulating literature on this absorbing topic a word from so high an authority would have been welcomed by the profession. That roentgenology is entitled to such consideration is shown, for instance, by the fact that Götzky, at a meeting of the Southwest German and Lower Rhenish-Westphalian Society for Pediatrics, in 1913, presented a large number of roentgenograms showing syphilitic bone changes in children in whom no clinical symptoms of the disease had been detected.

The literature, although necessarily still of a comparatively recent date, deals with the congenital and acquired forms of syphilis affecting the human anatomy; it describes and illustrates the signs by which they can be detected, furnishes valuable pointers in the differential diagnosis between certain affections, and demonstrates the fact that roentgenology is not only valuable in supporting or refuting the clinical diagnosis, but also in clinching it when ordinary methods of examination fail to be decisive.

Among the more recent contributions dealing with the general subject of roentgen diagnosis of luetic lesions is one by Blaine, who states that syphilitic lesions which attack the osseous tissue occur in the hereditary and tertiary stages, and present the least difficulty to their demonstration. In soft tissues, he continues, the roentgen diagnosis is precarious.

### SYPHILIS OF THE BONES

After describing the principal roentgen findings of syphilitic bone lesions, this author states that in syphilis of the periosteum the shadow

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may vary from a slight erosion to extensive raggedness, but it is difficult to distinguish roentgenologically between periosteal syphilis and simple inflammatory periostitis. The clinical history and the Wassermann reaction should always be taken into consideration. A subperiosteal gumma will distinctly lift the periosteum, while in luetic osteitis the bone cortex shows marked hypertrophy, resulting in raggedness and furring. Syphilitic joint lesions may show a considerable amount of destruction and involve the epiphyseal area. In conclusion, the author enumerates some differential roentgen points between syphilis and osteomyelitis, tuberculous osteitis, bone abscess, gout, sarcoma, carcinoma, and osteitis deformans.

In this respect Brickner deals particularly with the roentgenographic diagnosis of syphilis, tuberculosis, tumors, and osteomyelitis of the long bones. He states that syphilis of the bones is essentially an inflammation of the periosteum alone or of the periosteum and the bone itself. The most distinguishing features are thickening of the periosteum and of the bony tissue, especially the cortex, both of which produce black shadows. A light area is produced by gummatous destruction of the bone.

The periostitis may appear in scattered areas or along the entire length of the diaphysis, but the shadow is not always localized (as Brickner states), but may partake of quite a general character. Syphilitic periostitis begins next to the bone as a subperiosteal infiltration, so that the periosteal shadow, which in the early stages is usually narrow, is lifted away from the bone. In advanced conditions, as in localized periostitis gummosa, the shadow acquires considerable density, while a palpable periosteal gumma, being only inflammatory, causes no shadow.

Bone destruction due to gummas produces light areas surrounded by a dark shadow of reactive bone thickening, which differentiates this condition from osseous tumors and tuberculosis. When a gumma surrounds an island of bone, it appears in the roentgenogram as a sequestrum, but this is unusual in unmixed syphilitic osteomyelitis, which also contrasts it with tuberculous and pyogenic osteomyelitis.

Brickner quotes Hochsinger as describing the roentgenographic features of osteochondritis of hereditary syphilis. They consist chiefly in thickening and periostitis, with irregular absorption of bone at the epiphyseal end of the diaphysis, widening of the epiphyseal cartilage, the borders of which are jagged, and a callous shadow in the event of an epiphyseal separation.

As to the roentgenographic differentiation between (hereditary)

syphilitic and tuberculous dactylitis, Brickner quotes Ware substantially as follows: Tuberculosis originates in the epiphysis, syphilis in the epiphyseal end of the diaphysis. In tuberculosis, periosteal thickening is absent or nearly so—in syphilis it is marked. Tuberculosis has a great tendency to bone destruction, syphilis to bone production. Inflammation of the soft parts causes swelling in tuberculosis, while in syphilis this is largely due to thickening of the bone. Suppurating sinuses are often observed in tuberculosis, but only rarely in the syphilitic form. Multiple dactylitis may be syphilitic or rachitic, but not tuberculous as a rule.

Fraenkel is convinced that not only tubular but also flat bones with endochondral growth are subject to syphilitic ravages, having formed this opinion on his roentgenologic examinations of fetuses and infants, both living and dead. The flat bones are also involved in congenital syphilitic ossifying periostitis, the acetabulum particularly showing considerable osteophytic deposit. The ribs, likewise, were involved in all cases in which the tubular bones were affected, and, in view of the ready accessibility of the ribs to the eye, their examination would be the simplest means of obtaining information as to the presence of a syphilitic bone affection. Fraenkel considers it a direct law that there is no osteochondritis anywhere unless the ribs participate in it. He is not equally positive in regard to periostitis ossificans congenita syphilitica.

In a later article, dealing with epiphyseal detachment and congenital syphilitic osteochondritis, Fraenkel's observations differ considerably from those of Hochsinger. While the latter found the epiphysis of the distal humerus involved in six cases, Fraenkel has seen detachment of the epiphysis at that place only once. At the lower extremities Hochsinger has never observed a displacement between epiphysis and diaphysis, while Fraenkel has seen this condition in two fetuses and in a seven-weeks'-old infant, using the roentgen ray as the method of examination. There can be no doubt, therefore, the author holds that epiphyseal detachment at the lower extremities occurs also in living congenitally syphilitic children, although he admits that it predominates in the upper extremities.

Fraenkel emphatically contradicts Hochsinger's assertion that the osteochondritic process at the upper extremities develops most intensely and most frequently at the distal epiphysis of the humerus. This, he maintains, is at variance not only with the statement of Wegner, the discoverer of the disease in question, but also with the roentgenologic

examinations of the skeletons of congenitally syphilitic children, made by Fraenkel himself. Indeed, Wegner states that the lower epiphysis of the humerus is constantly the least affected part, and Fraenkel has observed its involvement only in a single case. Similarly, Hochsinger's statements as to the epiphyseal detachment of the distal humerus end are directly contrary to the results of anatomicoroentgenologic examinations.

Fraenkel further disputes Hochsinger's contention that the absence of reactive manifestations in detachments, as seen in stillbirths, is a regular occurrence. Similarly, Hochsinger's statement that epiphyseal detachment in stillbirths is often found in all tubular bones, whereas in infants several weeks old only one or a few epiphyses are detached, is, according to Fraenkel, contradicted by roentgenologic examinations in which rough handling is out of the question. The detachment occurs in different directions, oblique or transverse, but never at the borderline between diaphysis and epiphysis, as stated by Hochsinger.

Another point on which these two authors differ concerns the roentgenologic visibility of hereditosyphilitic epiphyseal detachment, which Hochsinger denies, while Fraenkel maintains that the roentgen method is simple, elegant, and reliable, not only in regard to establishing the occurrence of the condition, but also in the following up of the curative process.

Fraenkel claims to have discovered the roentgenologic fact consisting in the observation of the involution of osteochondritic manifestations under the influence of antisymphilitic therapy.

The bones in congenital syphilis also form the subject of an article by Post, the object of which is to show by a number of roentgenograms that the pathologic processes observed by pathologists in the pre-roentgen era may be confirmed by roentgen plates. This refers particularly to the line of ossification, spoken of as osteochondritis, which was first described by Wegner in 1870. The infantile changes due to pseudoparalysis or Parrot's disease are recognized quite early by the roentgen rays and allow of a diagnosis of syphilis in some cases of stillbirths without a necropsy. How long it is possible to trace the effects of this osteochondritis in older children is not yet determined.

The thickening of the cortex of the long bones as a result of periostitis is well marked in a great many cases and of great value in the diagnosis of doubtful cases. There may also be periosteal changes as occur in the acquired form, as well as osteoperiostitis and gummas.

Certain changes in the bone, analogous to osteomyelitis, are not always easy to recognize as due to syphilis and are often regarded as tuberculous or purulent infection.

Diefenbach has shown that in congenital syphilis there is periosteal enlargement about the metacarpal bones or phalanges, or the metatarsal or tarsal bones may be affected similarly. The periosteal shadow appears like a cloak hung about bone, and this dark envelop is characteristic of congenital syphilis.

Syphilitic periostitis or gummatous periostitis presents the following points in roentgenologic diagnosis:

1. Irregular contour of periosteum.
2. When the continuity of the periosteum is destroyed the tissue appears as if moth-eaten or reticulated.
3. Sclerosis of bone with increased shadow of the bone is always an accompaniment of syphilitic invasion.
4. In certain locations, as the anterior surface of the tibia, a curve or bow-like protrusion is formed, due to the bulging out of the periosteum.

Differentiating these diagnostic points from other bone lesions, the author mentions the characteristics of periostitis due to infection or trauma, non-syphilitic osteomyelitis, peripheral sarcoma, and tuberculosis of the bone.

Cameron reports the case of an infant, six weeks old, in which the roentgen rays showed increased thickness of the periosteal bone, the outlying masses of bone lying beyond the outline of the shaft, and the irregular shadow of the line separating the epiphysis from the diaphysis. He classifies this case as one of syphilitic epiphysitis of the lower end of the right femur and mentions the peculiar facts that there were no obvious clinical symptoms of the disease, that the patient's twin brother showed no clinical evidence of syphilis, but that both infants and the mother gave a positive Wassermann.

To the late Bela Alexander we are indebted for two communications on syphilis of the fetal spinal column. In his first communication he has shown that it is possible to visualize roentgenographically the finest details of syphilitic development in the fetal bones, and that some of these details are so fine as to be macroscopically indistinguishable. His studies have shown much that was new in the development of fetal bone and in fetal pathology generally.

In his second communication Alexander deals with the syphilitic changes in the ossifications of the massæ laterales and sternum, at the

same time discussing the development of syphilitic changes in the fetal diaphyseal ends.

The point the author makes in his first article is that syphilis does not interfere in any way with the regular occurrence of the osseous points—the incipient and further development of the ossifications. But when such development has progressed to a certain degree, where the inner structure commences to shape itself in the cartilage which is partly inclosed in the perichondral, periosteal ossification, the picture of enchondral bone fibers or trabeculae is distinctly traced by the roentgen rays, and with it the characteristic marks which indicate the syphilitic changes.

In about 60 congenitally syphilitic children with positive Wassermann, Dünzelmann and Schmidt found that the roentgen rays demonstrate nearly always osteochondritic and periostitic bone affections of the extremities, even when no signs point to clinical changes of the bones. The authors strictly distinguish between epiphyseal, secondary periosteal and diaphyseal periostitis, the latter being an osseous affection independent of osteochondritis which always points to an advanced stage of syphilis.

The scabbard-shaped tibia, or Fournier's *tibia en lame de sabre*, is discussed in Professor Axhausen's contributions to bone and joint syphilis. This unshapely thickening and arching of the tibia has been considered pathognomonic for hereditary syphilis. The fundamental change of the osseous structure is reflected in the roentgen findings which confirm the loss of division into a smooth compacta and a medullary cavity. Instead, there is a uniform, usually distended, diffuse, spongy bone shadow. Not infrequently remnants of the compacta in the course of transition may still be recognized within the diffuse shadow, and in such cases the gradual disintegration and wasting of the old bone may be observed with considerable distinctness.

Codman states that in the late forms of hereditary syphilis other bones are rarely found affected unless tibias are also affected. Extreme cases give a "saber-shaped" tibia, but when this condition is present, the fibula also shows localized areas of cortical thickening. There may be a "bone blister," due to localized gummatous formation under the periosteum. Occasionally there is localized destruction of bone substance on the diaphyseal line, but when this is so, there is also increase of the cortical bone in some portions of the shaft. Interference with epiphyseal growth may cause relative shortening of ulna and radius.



Fritsch deals with the same subject from a different angle. He describes a case of scabbard-shaped tibia as illustrating the fact that this anomaly may be the result of acquired syphilis in the adult, provided external local irritation conduces to the production of favorable conditions. This happened in the case of a woman, fifty-four years of age, who had been infected by her husband, but showed no other clinical syphilitic signs but the tibial convexity. She had been in the habit of steadying herself against the edge of the bed when lifting her husband and this caused a "blister" and subsequently a thickening of the tibia which in the course of time assumed a bulging curvature. This was associated with severe paroxysmal pains in the leg and knee-joint which greatly interfered with walking. The Wassermann was positive.

The roentgenogram at once revealed a striking curvature, elongation and thickening of the tibia, forming an arch over the perfectly normal fibula. The osseous structure of the tibia was markedly changed. As a whole, there was pronounced condensation of the osseous substance interrupted, however, by irregular transparent surfaces of elongated form and again surrounded by particularly dark shadows. At the edge there were irregular periosteal deposits, especially toward the upper region; distally the tibia merged into normal form and structure.

A case of late hereditary syphilis is reported by Badin in a six-year-old girl whose right knee was in pronounced valgum position. There were no pathologic manifestations up to the age of thirteen months, when the right knee became swollen and the lower leg turned outward, without causing any pain either at rest or when walking. Since then a number of physicians instituted various treatments, all of which served to exaggerate the condition. The family history elicited nothing specific with the exception of a gonorrhea which the father contracted eleven years previously. The clinical examination of the patient revealed numerous other skeletal deformities and the roentgen examination furnished the following findings:

The upper and lower regions of the femoral diaphysis of the right leg were enlarged, deformed, and pervaded by numerous foci of rarefying osteitis. The two condyles had a downward and inward direction: and the greater part of the epiphyseal cartilage seemed ossified. There were osteoperiostitic lesions of the tibia, and the articular surface was deflected downward and outward. Traces of rarefaction were also found on the upper part of the perineum. The upper part of the femur was swollen, especially toward the inner side, and deformed. The head of the femur

was in complete anteversion, the neck in the coxa valga position. The entire osseous substance in this region was extremely rarefied. The iliac bone was maldeveloped, serrated, and thickened. The os pubis also showed rarefaction. The bones of the hands were similarly affected.

From these findings the author concludes that the genu valgum was merely a symptom of hereditary syphilitic ostitis, after excluding chronic osteomyelitis which would have been accompanied by fever, violent pain and abscess. Tuberculous ostitis would have involved the articulation long ago; the evolution and roentgenologic appearance of osteosarcoma are totally different; and osteopsathyrosis, osseous cysts and osteomalacia were similarly ruled out. When, moreover, the Wassermann test proved positive, the necessary treatment was instituted. Ten months later the reaction was negative and remained so, although the treatment was discontinued when this had effected a change as favorable as could be expected.

Pied reports two cases of syphilitic Pott's disease.

The first patient, a man fifty-seven years of age, had previously been cured of facial paresis and lichen planus by specific treatment. These complaints have returned, but as they do not cause any pain, the patient pays no attention to them. On the other hand, he has suffered for thirty years exceedingly painful neuralgic crises, the pain occurring in the body below the shoulders, very rarely in the arms and legs, and never in the neck or head. The pains are worse at night and defy all medication.

Physical examination revealed two large curves from the fifth to the twelfth dorsal vertebræ, kyphosis and scoliosis, with the convexity to the right. Deep pressure there produced an anxious feeling. These and other clinical findings prompted a diagnosis of very slow curving of the spinal cord under the influence of syphilis. Antiluetic and orthopedic treatment was instituted with the result that the general condition of the patient improved considerably while the curvature of the spine remained.

A colleague made the roentgenologic examination without having been informed of the suspected syphilis, the patient's transportation for that purpose having been previously impossible. The roentgenogram confirmed the spinal lesion at the indicated place. The vertebral bodies were less dense than the others and showed differences in hue. The absence of intervertebral spaces was particularly striking. The entire mass of bone seemed to consist of one piece of non-homogeneous density.

periostitis, the thickened, striated appearance of the periosteum being almost pathognomonic of syphilis.

Brickner, in his article previously referred to, writes with reference to syphilitic joints that, when the osseous tissues are clearly invaded they produce the same type of shadows as in syphilis of the shaft, periosteal involvement, and bone production. Gumma of the articular surface of a bone is recognizable, while destruction of the articular surface by gummatous chondritis is less easily distinguished. Bilateral arthritis and synovitis points to syphilis rather than tuberculosis.

Ely, in an article on diseases of joints and bone-marrow, believes that syphilitic arthritis is often mistaken for other affections and proceeds to give a description of it. He mentions two well-differentiated forms which correspond to the synovial and bony forms of joint tuberculosis and probably to two others: the multiarticular variety and Charcot's joint.

The rarer form of joint syphilis is a synovitis which occurs in the tertiary stage, usually in the knee, without any tendency to involve the bone, unless as the result of unwise operative measures. The author shows the roentgenogram of the knee-joint of a child after treatment for two years, with a diagnosis of tuberculosis. The illustration shows the diseased tibial epiphysis and the proliferating osteitis of the femoral shaft at about four inches above the joint. A second roentgenogram shows the improvement in the tibial epiphysis and the gouged-out appearance in the femoral epiphysis four months later, after two injections of salvarsan and a course of mercurial inunctions.

A more severe and more frequent form of syphilis occurs as a proliferating inflammation of the marrow and inner layer of the periosteum, with or without an inflammation of the synovial membrane. Not only are the clinical pictures of this affection and joint tuberculosis often the same, but an expert roentgenologist may not be able to distinguish between them, so that other signs of syphilis must be depended on for a differentiation.

The multiarticular form occurs almost certainly as a late syphilitic manifestation. Several roentgenograms illustrate this form by the swelling and flexion of the fingers, the superextensions of the phalanges, the rarefactions and destruction of the bone ends, and the bony ankylosis. In one case the wrist bones and the radii were involved, and in another all the interphalangeal joints, with bony outgrowths.

## CHARCOT'S JOINTS

In the diagnosis of Charcot's joint Ely does not mention the use of the roentgen ray. Further information on this subject can be gleaned from Case's article on the roentgenology of chronic joint diseases. According to this author, roentgen-ray findings in early syphilitic involvement of the joints are not characteristic. Unless there develops a synovial effusion or unless evidences of characteristic osteoperiostitis are discovered, the findings are not likely to be different from those of acute articular rheumatism.

Ely quotes Redard as mentioning the following diagnostic characteristics: Clear blotches at the level of the epiphysis, indicating the presence of an interosseous gumma and the evidence of a rarefying ostitis, the increase in the circumference of the bones seen especially in the epiphyseal region, the osteophytes, the irregularity of certain portions of the bones, and spontaneous fractures.

The roentgenogram does not record the exact size of gummatous deposits which are not ossified, since new-formed bone is still permeable to the roentgen ray. The ossifying process involving the capsule gives rise to a varying quantity of osseous débris within the joints, well shown in roentgenograms of typical cases.

From the x-ray standpoint the typical findings in tabetic arthropathy are the extensive proliferating and destructive processes which run a parallel course and lead to extracapsular ossifications due to bone formation in the fibrous layer of the joint capsule. Fluid in the joints, subluxations, and pathologic fractures, and often the absence of pain on motion, are other diagnostic features of importance. The bone lesion sometimes resembles sarcoma.

In incipient cases differential diagnosis is difficult. The absence of pain is a constant finding in these cases, yet in some instances the movements of the joints are exceedingly painful.

In the tabetic form of syringomyelia, arthropathy occurs in about 10 per cent of the cases. Thickening of the bones in the region of the epiphysis, osseous layers which are poor in calcium salts, an atrophic condition of the bones, and occasional joint symptoms sometimes appear on account of interference with the trophic impulses.

According to Blaine, Charcot's joint has a rather characteristic roentgen appearance. The changes vary from a slight irregularity of outline which may be difficult to distinguish from an early arthritis,

to an enormous joint destruction in which all resemblance to the normal joint has been lost.

According to Young, Charcot's joint is characterized by destructive atrophic changes in the epiphysis from friction, which are mechanical in character. The symptoms of tabes dorsalis are so characteristic of the syndrome so easily recognized that the diagnosis of this condition is quite apparent to the intelligent diagnostician.

Matsuoka contributes an extensive article on the subject of articular affections in tabes dorsalis. He concludes that it is probable that the nerves supplying the joints participate in such a process of degeneration, leading to a secondary infection of the joints. He thinks it probable that osteoarthropathia tabica is caused by the affection of the nervous system.

#### TABETIC AFFECTIONS

Krüger likewise contributes a detailed article on the subject of tabetic arthropathy. He thinks that, although the diagnosis in advanced cases is not difficult with the aid of a roentgen examination, there are certain incipient articular affections that are difficult to differentiate.

There are also cases of arthropathy which commence with a slightly atypical articular fracture. This happened in a healthy man of thirty-seven years, who had slipped on a banana peel, sliding with the left knee forward and kinking in the right knee, without falling down. The knee-joint was swollen without effusion. There were pronounced lateral mobility and distinct crepitation below the knee-joint. The roentgenogram showed a small scattering of bone. After two months' treatment the patient was discharged free from complaints. Seven months later considerable effusion had taken place in the knee-joint, and a roentgen examination disclosed a very rapid progress of tabetic arthropathy. The classic signs of tabes were not yet present, but the diagnosis was made on the strength of the roentgenogram and the positive reaction of the Nonne test of the lumbar fluid.

Another case of tabetic joint affection without classic symptoms in a woman fifty years of age, was observed by Professor Koenig, according to Krüger's paper. The roentgenogram showed advanced tabetic arthropathy, periarticular ossifications, and destructions at the condylus internus femoris.

Krüger's experience goes to show that extensive proliferating and destructive processes, running an almost simultaneous course and lead-

to considerable extracapsular ossification, are typical roentgenohic signs. While the fact that the process may commence with an **ous lesion** is not yet generally known, this can often be distinctly in the roentgenogram. There are cases of tabetic arthropathy in which no clinical signs of the general affection are at first apparent, but **ome evident** at a later stage. In these cases of incipient tabes the evidence of the roentgen rays and positive Nonne reaction is of **icular importance**.

Garman in 1911 summarized the opinions and reports on tabetic osteoarthropathies of 96 previous writers. Bibliographic references are attached. He also reported eight cases from his own practice, illustrated by ten roentgenograms. In all of these the roentgen ray gave information of value either by determining or confirming the diagnosis or by contributing details. In no case did the joint trouble antedate other tabetic phenomena. In all cases but one the lesions were all advanced, and in that one the pathologic changes were shown in the wrists at an early stage of the disease. The marked roentgenologic features of Charcot's joint were summarized as follows: (1) Atrophy of the articular cartilages; (2) irregular destruction of bone, often associated in the same joint with (3) irregular hyperplasia of bone; (4) detached bone masses and detritus, and (5) translucent areas. He concludes as follows:

"1. With rare exceptions tabetic osteoarthropathies may be diagnosed by roentgenography alone.

"2. Only by the rays may detailed information be obtained as to the extent of involvement in tabetic joints.

"3. The roentgen rays will show joint lesions in tabetics, when ordinary clinical examination will not.

"4. The joints of all tabetics should be roentgenographed in the interest of the patient and in order that the earliest signs and manner of onset may be further elucidated.

"5. All joint lesions, except the very few in which the diagnosis is beyond doubt, should be examined with the roentgen ray."

Bering, in a paper on articular affections in acquired syphilis, states that certain affections of this kind cannot be referred either to early or late syphilis. In all probability articular syphilis has its primary seat in the articular capsule, but the diagnosis is not always easy. If it can be made early, the prognosis is favorable. Untreated cases will end in grave articular disturbances.

In his clinical experience the author has applied roentgenology with a view to facilitating the diagnosis, but he succeeded only in a few cases in demonstrating a slight separation of bones into fibers. Only in one of the cases had there been any extensive bone changes, and there was absolutely nothing characteristic of syphilis in any of the plates.

Coues, in a paper on syphilis and trauma, states that our present increased knowledge of the importance of roentgenograms of the skeletal system makes the detection of latent syphilis, which years ago would have been unrecognized, a comparatively simple procedure.

He calls attention to the fact that a roentgen examination may indirectly lead to the discovery of unsuspected syphilis, when only soft parts have been injured and their resistance to treatment suggests the aid of the roentgen ray in the search for a possible fracture.

Meriel reports the following case from the Hôtel Dieu, Paris, at the early period of 1899. An insignificant fall caused a fracture of the upper end of the humerus in a thirty-two-year-old porter, and roentgenograms revealed great rarefaction about the upper epiphyseal line of the humerus. It showed a juxta-epiphyseal fracture as well as an old fracture of the neck which had healed. The latest fracture was probably caused by muscular contraction with a rarefying specific osteitis of congenital origin, as the patient denied acquired syphilis. It is of interest that roentgenograms of an old fracture of the right humerus showed the same condition.

#### SYPHILIS OF THE AORTA

The methods employed for the demonstration of syphilitic aortic dilatation are inspection, palpation, percussion, and the roentgen method, and Kraus, in an article on the Heller-Doehle form of aortitis, shows that in the majority of cases there are roentgenologic signs which confirm the findings of the other clinical methods. Although the latter are generally sufficient to make a diagnosis, he advises resorting to roentgen control, whenever possible.

Syphilitic affections of the aorta also form the subject of a paper by Deneke, who discusses the rôle syphilis plays in the etiology. After enumerating in detail the clinical methods of establishing a diagnosis of aneurysm of the aorta, Deneke states that in all cases of difficulty a roentgen examination far exceeds in value all diagnostic methods, adding that through that examination about one-half of all cases of aneurysm are detected. With the use of the two oblique diameters a really plastic

picture of the aneurysmal sac can often be obtained on the screen. Only two sections of the aorta are not roentgenoscopically visible: one of these is the root of the aorta, which is located within the heart shadow, and the other is the concavity of the arch, in which only gross changes in the second oblique diameter may be recognized.

Eisler and Kreuzfuchs have a great deal to say on the roentgen diagnosis of syphilis of the aorta. Aside from a diffuse dilatation of the aorta, a characteristic sign in the roentgen examination of aortic syphilis is that a certain part distinctly bulges more prominently than the rest, and on comparing the roentgenograms of aortic syphilis with those of aneurysms, it will be found that the difference is only one of degree and not of principle. This is in full agreement with the experience of pathologic anatomists and the authors consider Kaufmann correct in stating that on inspection of the typical pictures of syphilitic aortitis one is impressed with the idea that from this picture to that of aneurysm is only a small step. A large collection of roentgenograms of aneurysms and syphilitic aortitis in the Roentgen Institute of the Vienna General Polyclinic enabled the authors to recognize for each type of aneurysm a perfectly analogous type of syphilitic aortitis.

In conclusion the authors mention the occurrence of cases of aortic syphilis with diffuse dilatation of the aorta, in which the roentgenograms fail to record any specific characteristics.

Lippmann and Quiring deal with the roentgen examination of aortic affections, giving special consideration to syphilis of the aorta. They describe the technic of visualizing the aorta in general, and in the second part they describe the result of their examinations of luetic changes of the aorta.

Turning to the findings of the luetic aorta in particular, 160 cases were examined in the course of eight years.

Comparing the results of fluoroscopy with those of roentgenography, it was found that in 107 examined cases 97 showed a deeper aortic shadow and 100 a greater lumen. This again confirms the fact that greater width and deeper shadow are a typical sign for aortic syphilis. It should be noted, however, that in fluoroscopy the width could not always be determined and frequently led to mistaken diagnosis. In most cases the aorta is erroneously assumed to be narrower than it is, and even aneurysms have been overlooked in some cases. The bulging of the pulmonary artery is particularly difficult to visualize and is consequently rarely diagnosed correctly. The shadow density, however,



can be roentgenoscopically well determined by the possibility of comparing it with that of the ribs.

Among the author's 160 cases, 29 aneurysms were found in the presence of diffuse distention of the aorta. In two of these patients a roentgen diagnosis of bronchial tumor and mediastinal tumor, respectively had been made, but the postmortems disclosed large aneurysms, one of which had compressed a bronchus. The valves were intact. The differential diagnosis between tumor and aneurysm often meets with a number of difficulties. The walls in aneurysms being usually considerably thickened and their cavities filled with thrombi, pulsation cannot ordinarily be demonstrated, and the clinical findings of the heart are frequently negative when the seat of the aneurysm is high, with the consequence that the true facts are revealed only at necropsy.

According to a report by Lieck, the roentgenogram of a young man suspected of incipient tuberculosis presented the following peculiar features: Pulmonary fields normal. Two lentil-sized glands at the right hilus at the level of the seventh posterior rib. Heart shadow normal. Descending aorta uniformly distended up to 8 cm. The aortic shadow exceeded the spinal column by 2.5 cm. to the right and 2 cm. to the left. The aortic arch participates in this uniform distention. Furthermore, the aortic shadow is elongated up to the jugulum. The intensity of the aortic shadow was very slight and transparent to the details of the spinal column.

This suggested syphilis, which was admitted, but supposedly cured. After a rigorous salvarsan and rest cure, another roentgen examination four and a half months later showed that the aortic shadow was no longer uniformly dilated but had irregular contours, among which a distinct bulging to the right suggested an incipient aneurysm. The aortic shadow had also become darker.

Lieck raises the question whether an aortic change of the above description may lead to aneurysm and whether specific treatment may effect an improvement or at least arrest.

Syphilitic aneurysm of the left upper division of the pulmonary artery is discussed by Warthin, who presented a case with a definite history of chancre and skin rashes, with Wassermann four positive, showing at necropsy syphilitic lesions in the heart, aorta, liver, pancreas, adrenals and testes; furthermore, atherosclerosis and aneurysm of the pulmonary artery, in the walls of which *Spirochæte pallida* were demonstrated. Syphilis of the pulmonary artery and syphilitic aneu-

rysm of the pulmonary artery are, therefore, for the first time conclusively demonstrated as pathologic entities.

A roentgenogram of the chest was also taken. The shadow of the aneurysm appears as a mass, somewhat larger than a hen's egg, on the left, extending from the second to the fourth ribs, fairly well descended on its outer border, but less well defined elsewhere. The density of the lung shadow on both sides is great, but more marked on the left below the level of the second rib.

The report of the roentgenologist adds that these shadows do not have the characteristics of tuberculosis or of ordinary inflammatory infiltrations; that the exact underlying pathology is not discovered but is suggestive of neoplasm.

#### SYPHILIS OF THE LUNGS

A roentgenologic contribution to syphilis of the lungs has been published by Kayser. It consists in the description of a case of hereditary gummatous syphilis of the lung which, aside from its rarity, is interesting because the author believes himself to have been the first to demonstrate roentgenologically the involution of gummatous syphilitic lung changes. The case is also of interest on account of its occurrence at the relatively late age of twelve years.

The first roentgenogram shows a considerable infiltration of the entire right middle lobe, with intense consolidations extending to the upper lobe. Nothing pointed to tuberculosis. The second roentgenogram was made two weeks later after inunctions with 30 gm. Hg had been applied. A distinct involution of the entire process was apparent, the originally dense shadows having cleared up and the process in the upper lobe especially having receded. The clinical picture underwent a corresponding improvement.

The third roentgenogram was made four weeks after the second, the specific treatment, having been discontinued in the mean time. The improvement of the condition was quite evident. The clinical improvement corresponded with the roentgen findings. It was clear from both the clinical and roentgenologic findings that the case was one of gummatous syphilis of the lung.

A report on two cases of syphilis of the lung comes from Bauch. Fluoroscopic examination showed marked dense bands of fibrous tissue over the entire right side. The left side was clear. The hilus glands were enlarged on both sides, and there were cavities and adhesions in

the upper half. There was pneumothorax in the axillary position in the upper half. The lower half showed a dense, peribronchial infiltration with marked density at the axillary portion of the base and with numerous enlarged bronchi. The quiet, evenly dense shadow at the lower axilla might be due to thickened pleura. The left lung is normal, except for the enlarged hilus gland. The mediastinum is displaced to the right. The right diaphragm is elevated and irregular. The ascending aorta is markedly widened. The heart is exceedingly small.

In view of the stationary condition, the lung involvement on the right and mostly at the base and roots, the negative sputum, the positive Wassermann, the comfortable feeling in spite of excavations, the afebrile course, the stationary weight and the typical location of metastatic affection in the roentgenogram, the inference was that the case was one of syphilis and not of tuberculosis.

A similar case, with a clinical diagnosis of incipient tuberculosis, showed the following roentgen findings: The entire left lung showed markedly diminished aëration apparently due to diffuse peribronchial infiltration, most marked at and around the hilus and along the left border of the heart toward the base. The right lung failed to show any changes, except for a few small calcified glands around the hilus. Almost all the costal cartilages appeared calcified. There was bulging of the right diaphragm. The ascending aorta appeared dilated.

The following facts appeared sufficient proof for diagnosing this case as syphilis of the lung rather than tuberculosis: (1) Stationary condition of the lung instead of rapid tissue destruction; (2) stationary general condition instead of emaciation; (3) repeated negative sputum; (4) repeated positive Wassermann; (5) development of interstitial keratitis with improvement on mixed treatment; (6) roentgen findings showing that the roots were mainly involved and that the ascending aorta was dilated.

Watkins selects five cases to demonstrate the typical roentgen marking of lung syphilis, in three of which the suggestion of syphilis was made by the roentgenogram, and this was subsequently confirmed by the clinical course and the laboratory diagnosis. He advocates the routine Wassermann test for all tuberculous patients, as not less than 15 per cent in approximately 1000 chest roentgenograms showed the combined presence of syphilis and tuberculosis. As to differentiation, he states that lung syphilis must be differentiated from bronchiectasis, abscess, malignant tumors, pneumonokoniosis, unresolved pneumonia.

and tuberculosis. Bronchiectasis and abscess should not easily be mistaken for syphilis, since in them the cavity is a characteristic, while in syphilis absence of cavities is a peculiarity.

The lung shadow of pneumonokoniosis resembles that of combined syphilis and tuberculosis, and the probabilities are that any pneumonokoniotic patient with a positive Wassermann will have some foci of syphilis in the lung.

No roentgenologic differentiation can be made between lung syphilis and unresolved pneumonia, and the diagnosis depends on the clinical history and laboratory findings.

The recognition of differences between the shadows of syphilis and tuberculosis requires an intimate knowledge of the essential pathology of the two affections and their pathways of invasion into the lung. The shadows tend to show that syphilis invades the lower and middle lobes (contrary to Landis' statement), and tuberculosis the upper. In syphilis the densest shadow begins at the hilum and diminishes toward the periphery, while in tuberculosis characteristic shadows surround the apical or subpleural lobules. The shadows do not bear a distinct relation to the bronchi in syphilis, while those of tuberculosis are peribulbar and show a definite relation to some branch of the bronchial tree.

Syphilitic manifestations in the lungs, resembling pulmonary tuberculosis, have also been observed by Daniells and Dachtler. In a study of 150 cases of suspected tuberculosis of the lungs, extending over a period of ten years, the roentgenograms disclosed mixed infection of tuberculosis and syphilis in a few cases, while in eight cases the lung changes were due to syphilis. In all the cases tuberculosis was eliminated by Koch's tuberculin and by the fact that no signs of tuberculosis were demonstrated roentgenologically. On the other hand, the syphilitic infection was established by the history, clinical signs, Wassermann reaction, and antisyphilitic treatment.

The roentgen findings for syphilis of the lung were hardly characteristic, and their greatest value was in excluding tuberculosis. From a study of these cases the authors believe that a syphilitic condition of the lungs occurs more frequently than is usually suspected and that without doubt it is often treated for pulmonary tuberculosis.

Callender affirms that pulmonary syphilis gives a roentgen picture quite distinct from that of phthisis. The shadows, as in the same disease in bone, are clear-cut and sharp, with no tendency to mossiness of the borders and can be readily diagnosed by the roentgenogram.

This is denied by Watkins, who states that the shadow of syphilis has a very irregular border and that for this reason it cannot be mistaken for cancer, which gives a shadow with a sharp margin. In tumors of the lung the shadows are, according to Callender, homogeneous in appearance and lack the linear marking of the tuberculous lesion. The picture is quite distinct, especially in advanced conditions, and can be easily diagnosed.

Moore and Carman quote Rothschild as stating that pulmonary syphilis is shown in the roentgenograms as a diffuse shadow, but they have not seen any proved cases of pulmonary gumma, the possibility of syphilis having always been excluded by the Wassermann test.

Post reports two cases of syphilis of the lung, accompanied by roentgenograms. In both the dark shadow is confined to one side and the heart drawn toward the affected side. Both patients were syphilitic and in neither were tubercle bacilli found. The author adds that diseases of the lung, in which consolidation is found in unusual positions, or limited entirely to one lung in which tubercle bacilli have not been found, may be considered suspicious of syphilis. If the Wassermann is positive, the suspicion is much greater and may almost be regarded as a certainty. A diagnosis of tuberculosis under such conditions would not be permissible.

Holmes admits that syphilis of the lung is not well understood, although some types are fairly characteristic. Such is the case when one lung is largely involved without infection of the other, as this is not usually seen in tuberculosis. Moreover, in characteristic roentgenograms of acute syphilitic infections the changes are most evident around the larger bronchi and are less sharply defined than in tuberculosis. Calcification may not be present and the periphery of the lung is not involved.

#### SYPHILIS OF THE STOMACH

Turning to syphilis of the stomach in its roentgenologic aspects. In a previous article Carman has stated that the clinical symptoms of gastric syphilis alone are not sufficient to distinguish it from other organic or even functional disorders of the stomach, nor are the roentgen signs of themselves distinctive and pathognomonic. However, they furnish decisive evidence of gastric pathology and, in correlation with the clinical and laboratory findings, give indispensable aid in arriving at a diagnosis. In describing the roentgenologic characteristics of gastric

syphilis, he has given special attention to the differentiation from cancer, stating that, if the filling defect is associated with a corresponding palpable mass, the whole picture would be easily mistaken for cancer but for considerations as follows:

1. Notwithstanding the extensive distortion of the stomach, no corresponding mass may be felt, and the filling defects are evidently due, not to the intrusion of a tumor, but to an infiltration and contraction of the gastric walls.

2. The roentgenologist may be impressed by the discrepancy between the extent of gastric involvement and the general condition of the patient, who is often below the cancer age, is anemic rather than cachectic, gives a longer history than that commonly given by cancer patients, and, on the whole, is not ill in proportion to the extent of sickness as shown by the roentgen ray.

3. The infrequency of a six-hour residue of the barium meal in syphilis is noteworthy. While in cancer of the stomach the six-hour retention occurs in 60 per cent of the cases, and in gastric ulcer in 50 per cent, such residue is only rarely seen in syphilis of the stomach. But even with these points in favor of a diagnosis of gastric syphilis, the latter should be confirmed by a Wassermann test and examination of the spinal fluid.

Since this article was written, the writer's experience has been that in many of these cases the roentgen findings which had previously only been noticed as important enough for further study and observation, positively furnish characteristic information on which a roentgen diagnosis may be based. The points are precisely those mentioned in this article, and the writer has convinced himself that they furnish reliable guides. This does not mean that he would commit himself to 100 per cent correct diagnoses, but among the cases which have since come under his notice there have been several in which a diagnosis of gastric syphilis was made on the strength of the roentgen findings alone, such diagnoses having been afterward confirmed by the clinical history, serologic tests, and the effect of specific treatment.

Thus, although it is perfectly true that, up to a short time ago, syphilis of the stomach was more or less of a curiosity, nevertheless the more recent experience and studies of Downes, Le Wald, the writer, and others have culminated in the fact that the symptomatology and the methods of roentgenologic examination have been fairly thoroughly worked out. It is not easy to understand why there should be such a

discrepancy between clinicians and pathologists about this disease except on the assumption that patients regain their health and there is no opportunity for postmortem verification.

McNeil's opinion on syphilis of the stomach was formed at a time when practically all pathologists, as he states, seemed to consider it more or less of a curiosity.

On the other hand, Eusterman believes that the affection, though rare, is not as infrequent as is generally supposed. The possibility of its presence should be considered in every atypical case, and the diagnosis may often be accidental, but the aid of the Wassermann reaction and the roentgen rays is necessary to establish the specificity of the lesion. The fallacy should be avoided of considering a gastric lesion necessarily luetic in the presence of a consistently positive Wassermann, because syphilis may coexist with benign and malignant gastric disease. The rôle played by syphilis in the etiology of gastric ulcer is doubtful not only because of the rarity of the cases in which the two are associated, but also because of the results of Rosenow's research work in regard to the streptococcal origin of gastric and duodenal ulcers, and finally because of insufficient evidence to show that simple ulcer becomes gummatous in the presence of systemic or gastric syphilis. The author therefore considers the inclusion of roentgenology in the methods of examination as absolutely necessary to make an accurate differentiation between early syphilitic gastric ulcer and non-septic lesions of the stomach. To the roentgenologist, the combination of a gross filling defect in the absence of a palpable mass and six-hour barium residue, the tendency to hour-glass deformity, and the absence of a proportionate cachexia, suggest gastric syphilis. Technically, however, the author adds, such findings cannot always be differentiated from carcinoma.

Einhorn, in his further observations (1915) on this subject, includes the interesting report of a case of syphilitic tumor of the stomach which simulated cancer to the minutest detail. This refers not only to the clinical symptoms, but also to the roentgen examination. The patient was a forty-six-year-old negro, and the first roentgenologic report simply stated that there were symptoms of indurated pyloric ulcer. The report of a second examination six days later read as follows: "Partial defect in the pyloric part, stomach vertical, orthotonic. No residue after six hours. Intestinal hypermotility. Pylorus at the level of the umbilicus in the median line. The lesser curvature on the left of the median line." The roentgen diagnosis was, therefore, carcinoma of the pylorus. As

the Wassermann reaction was strongly positive, the patient was treated on antisyphilitic principles with complete success.

In another case the roentgen examination confirmed the clinical diagnosis of a dilated stomach and some irregularity of the duodenal cap, but was not sufficiently definite to justify a diagnosis. Large doses of bismuth and atropin failed to relieve the periodic attacks of severe vomiting, and gastro-enterostomy was already considered when, on account of the positive Wassermann reaction, antisyphilitic treatment was applied, which brought about a complete recovery.

A case of syphilitic hour-glass contraction is within the experience of Culler. This condition was diagnosed by several physicians as gastric or duodenal ulcer, and not until the roentgen and Wassermann examinations were made was the correct diagnosis of hour-glass contracture of the stomach, due to syphilitic ulceration, established.

Downes sends in a "Further Report of Eight Cases of Syphilis of the Stomach," which is an amplified rendition of the report by Downes and LeWald of over two years previously. According to these authors the diagnosis of syphilis of the stomach can be made with a fair degree of certainty, if the clinical and laboratory findings are given proper consideration. Acquired cases may be more difficult to diagnose than the congenital, but in both types the course of the disease differs from the simple gastric or duodenal ulcer. A positive Wassermann reaction with roentgenographic findings of persistent and unusual deformity of the stomach establishes the diagnosis beyond much doubt, although the value of the antisyphilitic treatment in confirming the diagnosis cannot be ignored.

The late Hunter McGuire is said to have stated that much of his success was due to treating patients for syphilis whenever their manifestations were obscure. In fact, Niles believes the same principle might apply with satisfaction to some of our long-suffering dyspeptics who have run the therapeutic gamut without relief. Niles reports a case in which the feature of interest was the difficulty to differentiate between cancer and syphilis of the stomach. Even the roentgenogram, unless interpreted in conjunction with the clinical investigation and the positive Wassermann, would have been misleading.

In a group of 600 cases of syphilis with strongly positive Wassermann White found forty-four with prominent gastric symptoms, after excluding patients with hepatic cirrhosis, gumma of the liver, nephritis, and tabes. Two cases were proved by necropsy to be cancer of the



once been called to the possibility of a syphilitic infection he will weigh these findings with all the other available evidences and tests before performing the operation. No doubt there are competent and incompetent roentgenologists, but Brickner himself admits in a different paragraph that "the radiographic features of bone syphilis are so characteristic that in most cases the diagnosis can be made from the x-ray plate alone."

Brown believes that the real use of roentgen rays in the general diagnosis of hereditary stigmas consists in the prominent part they should play in the general diagnostic overhauling, for instance, in the case of children who present the slightest evidence of such signs in the form of subjective symptoms which cannot be locally accounted for. Thus, he refers to photophobia or any other ophthalmic manifestation, headache, snuffles, sore legs, mental backwardness, skeletal asymmetry, etc. Syphilis in its acquired form will ever be a source of interest to the roentgenologist, but Brown predicts that the hereditary type will supersede it.

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## THE DIAGNOSTIC VALUE OF LOWERED BONE CONDUCTION IN SYPHILIS

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Various writers have called attention to the importance in the diagnosis of syphilis of a test based on the difference in the perception of sound conducted through bone, as compared with an otherwise normal hearing test. The present study was made not only for the purpose of studying the reliability of such a procedure as an aid in diagnosing syphilis, but also to compare its efficiency with other means of recognizing the disease.

Extensive studies have been made on the syphilitic involvement of the eighth nerve, and on lowered bone conduction in syphilis, but methods and interpretations have differed materially from ours. Our investigation was suggested to us by the work of Oscar Beck, Wanner, and Willcutt, who had, however, confined their observations largely to cases in the early stages of the disease. Wanner was able to make a diagnosis of syphilis in 95 per cent of the cases he examined, before the appearance of general symptoms. The diagnosis was later confirmed by positive Wassermann reactions and other characteristic findings. Beck's examinations were made largely in early cases, but he had occasion incidentally to examine a limited number of patients with varied manifestations in all stages of the disease. In Beck's cases the phenomenon proved to be positive in the primary stage in only a few instances, and he believes that it manifests itself after the infection changes from a local to a constitutional one. Some of his florid eruptive cases gave a negative test. He contends, on the basis of his investigations, that the test is reliable in a high percentage of cases. Willcutt, on the basis of 293 cases of syphilis, most of them in the primary and secondary stages, with a few latent cases, subscribes to the value of the lowered bone-conduction test.

The method employed in our observations was as follows: Hearing tests were done routinely by the otologist (Barlow) in a number of cases

in which he was unaware of the diagnosis, and 100 cases were then selected in which the data were sufficiently complete to establish or exclude the presence of syphilis.

### THE LOWERED BONE-CONDUCTION TEST

The technic of the hearing test is not at all complicated and does not necessarily require special otologic training. Three tuning-forks are necessary: one whose vibration rate is 128 per second; one, 256; and the third, 2048. The forks are set in vibration either by striking rather vigorously, or by striking the fork on the knee or on the palm of the hand. The examiner holds the fork close to the ear of the patient until the patient no longer hears the sound. The examiner, taking his own hearing for normal, then carries the fork to his own ear to ascertain the patient's discrepancy, if any, and expresses in seconds the difference between the time the patient hears the fork and his own hearing of it.

*Part 1.*—After examining the ears of the patient for other pathologic conditions the 128 fork is set in vibration and is placed on the vertex of the skull of the patient, equidistant from the ears, and note is made of the equality of the tone as heard in both ears. Should there be a marked difference between the two ears, this must naturally be taken into account in any further examination and in the final interpretation. This test is known as the Weber test.

*Part 2.*—The fork used in the first test is set in rapid vibration, but this time it is simply held near the ear of the patient until he no longer hears it. The number of seconds that the patient hears the fork is noted. The examiner thereupon listens to the fork himself, noting the number of seconds that he hears it. Both ears are tested in this way, giving the value of the low limit. The 2048 fork is then used in like manner, giving the high limit of the patient's hearing.

*Part 3.*—This is the most important phase of the test—the comparison of the conduction of sound through bone in the patient, as compared with that in the examiner. The 256 fork is set in vibration by striking smartly against the palm of the hand, and the stem of the fork is held firmly to the mastoid process at about the level of the superior margin of the external canal, and just behind the ear. The patient is asked to note carefully when he no longer detects the tone of the fork, at which time the examiner conveys the fork to a corresponding position on his own mastoid, and carefully observes whether he hears the fork longer than the patient, and if so, how much longer. The number of

seconds the operator hears the fork after the patient ceases to hear, is expressed in terms of the patient's deficiency as minus seven seconds or minus eight seconds, or whatever the numeric value may be found to be. If the patient hears the fork through bone longer than the examiner, he has an increased bone conduction, which is designated as plus whatever the number of seconds may be. If the patient does not hear the fork as long as the examiner, the patient's bone conduction is said to be decreased or lowered. This test is performed on both ears and constitutes the Schwabach test.

*Part 4.*—The Rinné test is next done, which consists of comparing the conduction of sound by bone in the patient with his air conduction. This is obtained by holding the fork opposite the patient's external meatus after he has ceased to hear the sound through the bone. The test is essential to classify the type of deafness if any be present. Normal hearing shows air conduction of longer duration than bone conduction, and is called a positive Rinné test. The acuity of hearing may be tested for whispered voice, but this is not essential, as the bone-conduction test is a tuning-fork test.

If the examination of the ear does not show a preëxistent lesion, such as chronic suppurative otitis; if the high and low limits of the patient are normal; if the perception of sound is about equal in both ears, and the Rinné is positive, but the bone conduction shows a decrease of five seconds or more, or is decreased out of proportion\* to the rest of the tuning-fork tests, the patient is said to have a bone-conduction sufficiently reduced in the presence of normal hearing to justify the assumption that he has syphilis. A decrease of four seconds is considered to be within normal limits, because it has been found that there is a physiologic discrepancy between the actual interpretation and perception of the sound. By repeated tests on the same person one of us (Barlow) found that the person becomes educated to interpret more accurately the vibration of the fork, and that a person at first showing a reduction of four seconds, by repeated trial and after overcoming his first nervousness will very often show practically no reduction.

In the carrying out of these tests the patients were always examined

\* A hearing test showing Rinné positive, the 128 fork reduced fourteen seconds, high limit tested by the 2048 fork, reduced seven seconds and bone conduction reduced six seconds would not be indicative of syphilis because the bone conduction is not lowered out of proportion to the rest of the hearing test. Such a result indicates a true nerve or internal ear deafness. In a hearing test showing Rinné positive, low limit or the 128 fork reduced fourteen seconds, high limit or the 2048 fork reduced six seconds, but the bone conduction reduced ten seconds, we are justified in considering this test indicative of syphilis because the bone conduction is lowered out of proportion to the rest of the test.

in the same room, with the same set of tuning-forks, at about the same time of day, and by the same otologist. The perceptive power of the patient was also considered.

### CLINICAL METHODS EMPLOYED

The diagnosis of syphilis was established or excluded by an investigation as follows:

1. *The history*.—This was taken in considerable detail, since it has been our experience that important points, such as the presence in the past of a suggestive eruption, a persistent sore throat or mouth, falling of the hair, the taking of Wassermann tests previous to present examination, etc., are frequently overlooked in a routine or hasty clinical history.

2. *Residual signs of syphilis*.—A special effort was made to include details frequently slighted in routine examinations. Suspicious scars on the skin and mucous membranes were searched for. Solitary nodular and infiltrative syphilitic recurrences on the skin were not overlooked. The presence of leukoplakia buccalis was considered a diagnostic aid, but the fact that this lesion may be of other than syphilitic origin was kept in mind. A perforated septum was regarded as significant. That this condition is not exclusively luetic was not, however, forgotten. Investigation for evidence of syphilis by neurologic examination, and by identifying old cardiac and vascular lesions, etc., was carried out whenever any doubt arose. Examination of the fundus of the eye was made in many cases for signs of old or recent syphilis in the form of chorioretinitis, perivasculitis, and primary optic atrophy.

3. *Laboratory tests*.—These included, of course, the Wassermann and the provocative Wassermann tests, following the technic described by Stokes and O'Leary. In all cases presenting symptoms suggestive of central nervous system involvement a complete examination of the cerebrospinal fluid was made. Patients with suspicious but not conclusive evidence of lues were given the benefit of a therapeutic test. This consisted in the administration of at least three doses of arsphenamin at weekly intervals, and usually about five injections of one-sixth of a grain of mercury succinimid per week, for from 15 to 20 doses. An equivalent of the latter in mercurial inunctions was frequently employed.

We compared, in our 100 cases—(1) Negative bone conduction results with negative syphilitic findings; (2) negative bone conduction results with positive syphilitic findings; (3) positive bone conduction results



with negative syphilitic findings, and (4) positive bone conduction results with positive syphilitic findings. We then compared the individual symptoms and signs in the known syphilitic cases with the bone conduction findings, in order to detect any striking correspondence between the ear tests and the luetic symptomatology. This comparison included: (1) An estimate of the value of bone conduction results in various types of early syphilis (chancere, secondary eruptive manifestations, etc.); (2) comparison of bone conduction results with the positive Wassermann in latent lues; (3) comparison of bone conduction results with diagnostic evidence of syphilis in the nervous system; (4) comparison of bone conduction results with diagnostic evidence of late cutaneous syphilis; (5) comparison of bone conduction results with diagnostic evidence of osseous syphilis, and (6) comparison of the positive and negative Wassermann findings throughout the series with the results of bone-conduction tests.

#### STATEMENT OF RESULTS

Positive bone-conduction tests (reduction of five seconds or more with normal hearing) corresponded to positive symptoms and signs of syphilis in the 100 cases taken at random, in 46 per cent, when syphilis was actually present in 59 per cent. This gives the positive test an efficiency, in known syphilis, of 78 per cent. The negative bone-conduction tests (reduction of four seconds or less), under the same conditions, corresponded to the clinical absence of syphilis in 21 per cent of the cases when syphilis was actually absent in 41 per cent. This gives the negative test an efficiency of 51.2 per cent in ruling out syphilis. The result compares very favorably with the accuracy of the Wassermann test, in the types of cases considered. The margin of error in the test as a routine diagnostic aid is indicated by the fact that in 20 per cent of the cases in which the bone conduction was reduced sufficiently to justify a suspicion of syphilis, no syphilis could be demonstrated, and in 13 per cent of cases in which syphilis was present the bone conduction was negative and contributed nothing to the diagnosis.

TABLE 1

AGREEMENT BETWEEN THE TEST AND OTHER CLINICAL AND LABORATORY SIGNS IN 100 ROUTINE MISCELLANEOUS CASES			
Bone conduction positive	46	Bone conduction negative	21
Syphilis present	per cent	Syphilis absent	per cent
DISAGREEMENT BETWEEN THE TEST AND OTHER CLINICAL AND LABORATORY SIGNS IN 100 ROUTINE MISCELLANEOUS CASES			
Bone conduction negative	13	Bone conduction positive	20
Syphilis present	per cent	Syphilis absent	per cent

In the early local or primary and the disseminate or secondary stages the bone-conduction test was unreliable, since the number of cases of any given type dealt with was too small to yield trustworthy results. In some instances there was an eruption and in others there was none. Of six early cases, three showed a sufficiently reduced bone conduction for a diagnosis and three did not.

In comparing the results of the lowered bone-conduction test with the Wassermann test in latent lues, it was interesting to note that the two tests corresponded in 80 per cent of our cases. There were 15 of this type with a definitely positive Wassermann test and other evidence of syphilis; 12 of these cases showed a sufficiently reduced bone conduction; 3 did not.

In cases presenting syphilitic involvement of the central nervous system the test also proved equally reliable. Twelve of the 15 patients studied showed a lowered bone conduction of five seconds or more. Of the remaining three, two showed a bone conduction four seconds below normal and one a lowered conduction of three seconds. It may be mentioned that the patient with a three seconds' reduction had been subjected to unusually efficient treatment.

All of six patients with late syphilis of the skin showed a bone conduction lowered sufficiently to suggest syphilis. In all of these the Wassermann reaction was negative. We feel that in this type of case a larger group might reveal interesting findings, showing the value of the bone-conduction test in suggesting the presence of syphilis even with a negative Wassermann test. It is granted, of course, that in cutaneous syphilis the test is of less value than in many other forms of syphilis, because the morphology of the lesion is often sufficient for a diagnosis.

In patients with syphilitic bone lesions the test proved unreliable. There were seven in this group. In four of these the bone conduction was negative (not sufficiently lowered) and in three it was positive. In several of the negative cases the tests were made repeatedly, and always gave the same result. Why, in this type of case, the test should not have had a greater value, it is, of course, impossible to state at the present time.

Ninety-four patients were subjected to both a bone-conduction test and a Wassermann test.\* Of 55 patients with syphilis, both tests were

\* The routine Wassermann technic of the clinic, carried out under the direction of Sanford, employs one Noguchi antigen and a rabbit-human hemolytic system, guinea-pig complement, and fresh, active patient's serum, with the usual controls. When more than one antigen was employed, two alcoholic extracts of syphilitic liver, a stock Noguchi antigen, and an alcoholic antigen, reinforced with 0.4 per cent cholesterin, were employed.

positive in 19. In 6 instances the Wassermann was positive and the bone-conduction test was negative; in 7 both tests were negative. In 23 the Wassermann test was negative and the bone-conduction test was positive. The test would thus appear to be an important aid in the recognition of syphilis which is Wassermann negative by the technique used, were it not for the margin of error represented by the frequency of the positive bone-conduction test in the absence of syphilis.

Of 35 cases in which syphilis was absent, its absence was confirmed in 19 (48.7 per cent) by both a negative Wassermann and a negative bone-conduction test. In no case in which syphilis was absent did both tests prove positive. It seems, therefore, that a negative Wassermann and a negative bone-conduction test is fairly satisfactory evidence of the absence of syphilis. The bone-conduction test was positive and the Wassermann test was negative also in 19 cases in which syphilis was absent, an error of 48.7 per cent as contrasted with an effectiveness of 78 per cent. In other words, the test has little routine diagnostic value taken alone, since 78 per cent of positives in syphilitics is discounted by 48 per cent of positives in non-syphilitics.

TABLE 2

SYPHILIS PRESENT IN 55 CASES			
Bone conduction positive	} 19 cases (34.6 per cent)	Bone conduction negative	} 7 cases (12.7 per cent)
Wassermann positive		Wassermann negative	
Bone conduction positive	} 23 cases (41.8 per cent)	Bone conduction negative	} 6 cases (10.9 per cent)
Wassermann negative		Wassermann positive	
SYPHILIS ABSENT IN 39 CASES			
Bone conduction positive	} 0 cases (0 per cent)	Bone conduction negative	} 19 cases (48.7 per cent)
Wassermann positive		Wassermann negative	
Bone conduction positive	} 19 cases (48.7 per cent)	Bone conduction negative	} 1 case (2.6 per cent)
Wassermann negative		Wassermann positive	

## CONCLUSIONS

1. The so-called lowered bone-conduction test (reduction in conduction of sound by bone as compared with otherwise normal hearing) is positive in 78 per cent of known syphilitics in our series.
2. From the otologic standpoint, the test is of value only if a complete hearing test is done.
3. The efficiency of the test varied greatly in different types of syphilis, being at its best in late cutaneous syphilis (100 per cent), latent syphilis (80 per cent), syphilis of the central nervous system (80 per cent). It had almost no value in osseous lues, and the results in

syphilis were inconclusive (too few cases). A negative Wassermann combined with a negative bone-conduction test is strong evidence of the absence of syphilis.

4. The test agrees with the positive or negative diagnosis of syphilis 77 per cent, and disagrees in 23 per cent.
5. The test is also positive in 48.7 per cent of patients in whom syphilis could apparently be excluded.
6. It has, on the whole, therefore, only a restricted value as a diagnostic aid, owing to its high factor of error.

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amin anaphylaxis, may be made by way of Friedberger and Tsunoda's demonstration of the effect of fine precipitates in the blood-stream. Thus interpreted, the reaction to acid and imperfectly alkalized arsphenamin is anaphylactic shock due to the formation of a precipitate in the blood. Reasoning by analogy, the closely similar picture of nitritoid crisis may be anaphylactic shock produced by the formation of a precipitate in the blood.

The demonstration of the correctness of this reasoning has recently been accomplished by the work of Danysz and of Berman. Danysz has shown that the arsphenamin solution is essentially colloidal, and that on its injection the arsphenamin base is precipitated out by the constituents of the blood plasma, and then formed again into soluble organic derivatives. The rate of this precipitation is dependent to some extent on the alkalinity of the solution, and on the peculiarities of the individual blood plasma. If the solution is imperfectly alkalized, or if the serum of the patient is abnormal, rapid precipitation followed by acute reaction ensues. This observation links together the reaction to acid solutions of arsphenamin and the nitritoid crisis. Berman has recently shown that even with a properly prepared solution precipitation occurs in the serum of hypersensitive patients. He differs from Danysz, however, in believing that this precipitation involves the proteins of the serum rather than the arsphenamin base. He believes further that a tendency to nitritoid crisis can be predicted by testing the serum of a patient with a solution of arsphenamin before the injection is given.

The question as to whether the entire phenomenon of allergic reaction to arsphenamin may be explained either by insufficient alkalization of the solution or by peculiarities in the patient's blood-serum can certainly not be regarded as completely settled. There remains the large body of observation on variations in the toxicity of arsphenamin itself to be explained. The proposal of Schamberg and his collaborators that there is a factor in the preparation of arsphenamin, an impurity of as yet unknown constitution, present in the drug, is not at all incompatible with an allergic explanation of the reaction. It is conceivable that it is not the arsphenamin base alone which precipitates, but the serum proteins as well, and that this precipitation of the serum proteins may be accomplished with especial ease, even in comparatively normal persons, by a substance present as an impurity in the drug. No other satisfactory explanation can be found, to my mind, for the extreme frequency of reaction to certain brands of the drug, and its extreme rarity

under identical technical conditions, in others. On my own service, in which the operators and the technic of operation remain unchanged for months and even years at a time, there can be no other satisfactory explanation for the fact that during 5000 injections in which German preparations were used there were considerable periods when scarcely a day passed without a nitritoid crisis, while in 7000 subsequent injections in which arsenobenzol-Policlinic and novarsenobenzol-Billon have been employed the nitritoid crisis has become so rare that we have been compelled to all but abandon the work necessary to confirm the results presented in this paper. We have, moreover, had the opportunity to observe the production of crisis by an accurately alkalinized but evidently impure preparation used on the assurance of the manufacturers, in every one of five successive patients known not to present any personal idiosyncrasy to the drug. There can be little doubt in the minds of large users of arspenamin that there is a factor of toxicity and a tendency to the production of anaphylactic response in certain preparations which cannot be explained in absolutely general terms, and is probably due to specific impurities.

My own attempt to devise a protection against acute arspenamin reaction and incidentally to support the view that the phenomenon was a manifestation of anaphylactic shock consisted—(1) In an attempt to employ the well-known inhibitory effect of atropin, recently experimentally demonstrated, for example, by Pelz and Jackson in the dog, and (2) in an effort to induce antianaphylaxis to the drug according to the methods of Bezredka and Steinhardt. It should be noted that Swift had suggested the possibility of antianaphylaxis on the basis of a casual observation that if a nitritoid crisis set in and the injection were stopped, it could sometimes be resumed again in ten minutes without further ill effect. Work of this kind in patients can only be undertaken with an expectation of trustworthy results, when the idiosyncrasy for arspenamin is so definite and persistent that it is possible to exclude the factors of imperfect alkalinization, variations in the chemical composition of the drug as marketed, variations in the patients' individual state of health, and neurotic and hysteric factors. The number of patients meeting such control requirements is necessarily small, so that in a series of 12,000 injections it has been possible to employ the procedures described, with confidence in the results, in only about a dozen cases. The first case in which the method was employed is typical of the response in the entire series, and is here summarized. It should be

noted that in this case neosalvarsan was used, thus eliminating the question of proper alkalization of the solution so important in judging of a reaction to arsphenamin.

#### REPORT OF CASE

The patient was a rather stolid Swedish girl who took her idiosyncrasy very matter-of-factly. She was under treatment for a florid follicular secondary syphilid. Following her initial intravenous injection of neosalvarsan she exhibited a rather sharp Jarisch-Herxheimer reaction in spite of a moderate dose. The second injection at the end of a week was without reaction. After the third she developed a marked, unexplained rise of temperature. The interval between the third and fourth injections was then lengthened to two weeks, and the fourth injection passed without event. Following the fifth injection she again developed a marked rise of temperature and vomited. No further injections were given for six weeks. During her first course, then, this patient had shown gradually increasing evidence of intolerance of neosalvarsan.

The first injection of the second course marked the beginning of her nitritoid crises. Two minutes after the injection of three decigrams of neosalvarsan in concentrated solution by the method of Ravaut she developed, on the table, the characteristic intense scarlet flush, with edema of the face and neck, cough, stridor, asthmatic breathing, prostration, and vomiting. She recovered rapidly following a subcutaneous injection of ten minims of a 1:1000 solution of epinephrin.

On the next injection, one week later, the first attempt to protect the patient with atropin was made, a dose of  $\frac{1}{50}$  grain being given hypodermically fifteen minutes before the injection of neosalvarsan. The dose of neosalvarsan was six decigrams—double that of the preceding injection—and was given by the same technic. Only a very slight reaction occurred. There was no flush or pulmonary disturbance. The patient vomited once on returning to her room.

On the third injection, one week after the second, the dose of neosalvarsan was increased to seven decigrams, the dosage of atropin and the time interval being identical with that on the preceding occasion. This time the reaction was all but negligible, although the patient tasted and smelled the drug and was distinctly nauseated.

The fourth injection was given one week after the third, the dose of neosalvarsan again being seven decigrams. On this occasion, through a misunderstanding, the patient received only  $\frac{1}{150}$  grain of atropin

subcutaneously. That this dose was insufficient was promptly demonstrated by the occurrence of a crisis on the table, with marked flushing, edema, and vomiting.

Just preceding the fifth injection, also through a misunderstanding on the part of an assistant as to the size of the dose of atropin, the patient received  $\frac{1}{8}$  grain of atropin subcutaneously. The injection of neosalvarsan—six decigrams—which followed produced a mild reaction, with flush and vomiting.

So strongly did the efficiency of atropin in proper dosage suggest the anaphylactic nature of the reaction, that it was decided to attempt the production of antianaphylaxis in this case. Accordingly, one hour before the administration of the next injection of neosalvarsan the patient was given 0.05 gm. of the drug in one-half cubic centimeter of water intravenously. The neosalvarsan used was of the same control number as that employed for the previous injection, which had shown itself capable of producing marked reaction in this patient (Control V U J). Following the injection of the half decigram dose the patient became slightly dizzy and was a trifle nauseated on returning to bed. One hour after the preliminary injection the patient received 0.55 gm. of neosalvarsan intravenously in concentrated solution, injected at the usual rate. The complete inhibition of all reaction was striking. There was no flush, no nausea nor vomiting, no dizziness, cough, nor stridor. The eyes became slightly suffused. The patient felt so much better than usual as to astonish her and all those who knew of her reactions. She was returned to her room and no reaction was reported for twenty-four hours. At the end of this time, without rise of temperature or any other marked systemic symptoms, a generalized macular erythema of the typical late toxic type appeared. It was not accompanied by constitutional symptoms, and disappeared two or three days later. It was judged wise, however, not to invite an exfoliative dermatitis by any further arsenotherapy.

This case was surrounded by all the precautions against pseudoreaction that we could devise. The reactions observed were typical of the acute nitritoid crisis, and we felt that the sequence of events, as described, had not been modified by presuppositions on the part of the patient or by hysteric manifestations. Abundant objective evidence of the patient's intolerance was available. Not the least interesting suggestion based on these observations is the possibility that the acute anaphylaxis and the delayed toxic erythema are different types of reac-



tion. An antianaphylaxis which was developed to protect the patient against the former failed to protect against the latter complication. The influence of atropin seemed to be quite definitely a function of the dosage, and doses below  $\frac{1}{50}$  grain failed to protect the patient against shock. It is to be regretted that circumstances made it impossible to transfer the problem from the patient to experimental animals for a more thorough study.

Since its successful employment in the case described we have resorted a number of times to the induction of antianaphylaxis as a protection against acute arsphenamin reaction, notably in the treatment of patients with tuberculids, who show an idiosyncrasy in about 50 percent of the cases. I have noted with interest Danysz's impression, which my experience confirms, that small preliminary injections "vaccinate" the susceptible patient, so to speak, against the larger doses, an observation which Danysz supports by animal experiment, and offers likewise as a rationale for the regulation of dosage in treatment, and as a means for increasing individual tolerance of the drug.

#### SUMMARY

1. The acute "nitritoid" crisis or reaction to arsphenamin is a form of anaphylactic shock, explainable on physicochemical grounds as the result of a precipitation either of the drug from its colloidal solution, or of the colloids of the blood plasma, by the drug, or by an impurity. The reaction following the injection of an acid or only partially alkalinized solution of arsphenamin, either too rapidly or in too high concentration, is presumably of the same type.

2. The nitritoid crisis can apparently be inhibited by a previous injection of atropin ( $\frac{1}{50}$  grain), which further suggests that the reaction is a form of anaphylactic shock.

3. The induction of antianaphylaxis, as described above, further supports the belief that the nitritoid crisis is a form of anaphylactic shock.

4. The induction of antianaphylaxis in patients exhibiting persistent idiosyncrasy to arsphenamin or neoarsphenamin has proved clinically useful, and as a means of increasing their tolerance of the drug deserves further trial and study.

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# MEDICAL COÖPERATION IN THE PROBLEM OF WAR SYPHILIS\*

J. H. STOKES

The contact between the medical profession and the modern problem of syphilis is most direct and imperative at three points. If an effective public campaign against the disease is to be developed, there must be not alone the laws, rules, and penalties recently provided, but earlier and more efficient diagnosis of the disease, prompter and more effective treatment, and a new era of public enlightenment and coöperation.

## I. THE NEED FOR EARLIER DIAGNOSIS

Early diagnosis of syphilis is perforce a novel conception to many men who are practising medicine at the present day. For the older generation of medical men it had relatively little point, armed as they were with the feeble and ineffective weapons of mixed treatment *per se*, and the pea-sized inunction. To men with the older conceptions of the disease firmly rooted in them by a generation of practice, it must appear as heresy to insist that waiting until a secondary eruption appears loses the benefit of some of the most epochal advances in the history of medicine, and deliberately robs the patient of the one crucial opportunity for a cure of his infection. Yet this does not overstate the fact. The modern diagnosis of syphilis in the early primary stage, if possible, before the organism has spread to the lymphatics adjacent to the primary lesion, but at all events before the Wassermann reaction has become positive, is more far reaching in its medical and social significance than the finding of the tubercle bacillus in early tuberculosis. It is more significant because it points, not to a dubious prospect, but to instant and effective action. The institution of radical treatment of syphilis at this stage accomplishes what syphilologists term the abortive or radical cure of the disease. The first injection of salvarsan puts an immediate end to the

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infectivity of the patient. Within eight to twelve hours there are no longer any organisms obtainable from his lesions. Repeated injections of salvarsan, with intense mercurialization over a suitable period of time, seldom less than a year, seem to accomplish a sterilization of the body. I say seem, because no one can as yet rate the abortive cure of syphilis as a completely demonstrated fact, since such demonstrations have as their first essential, time. But the hope seems so reasonable, the undoubted tangible benefits in the form of a practically negligible period of infectivity, a greatly shortened period of treatment, and effective suppression of all bio-serologic evidence of the disease are so worth while, that it is no exaggeration to rate the possibility of abortive cure as paramount in the syphilology of today. This should be the treatment for tabes dorsalis and paresis, for syphilitic aortitis and chronic interstitial nephritis, for gummatous osteitis, for iritis, for interstitial keratitis—the treatment that *prevents*. Upon the first four to ten days of the primary lesion, while syphilis is still a practically local, banal infection, diagnosis should concentrate its every resource and treatment reach drum-fire intensity, for never again in the life history of the disease for the patient and his fellow-men will there be such another moment.

How has the profession reacted at large, thus far, to this most grave, most pressing responsibility? The *Spirochæta pallida* was recognized by Schaudinn and Hoffmann in 1905. Thousands of physicians who graduated up to 1910 have never seen the organism. A handful have seen it as a formal demonstration in the pathologic and bacteriologic laboratory. When I graduated from one of the best schools in the United States, I had seen one primary lesion, and that at a distance of forty feet. I had no idea that the discovery of the *Spirochæta pallida* had any vital clinical bearings, though I was vaguely aware that it had served as a scientific starting-point for the work of Ehrlich. I had never seen India ink in use in a clinical laboratory, to say nothing of comprehending the employment of the dark field. Yet I had a most thorough training in the diagnosis of tabes and paresis. In 1914 I demonstrated the spirochæte to a group of active practitioners, not one of them superannuated or unprogressive, who crowded around the microscope as men appreciating a medical curiosity rather than a vital fact in diagnosis and public health administration. Three years ago a medical survey of the dispensaries of New York City disclosed the fact that a negligible percentage of them had either the equipment or the men to diagnose syphilis by the identification of the causative organism. In 1911 in the United

States, army the ratio of cases recognized in the primary stage as compared with those allowed to proceed to florid secondary manifestations before a diagnosis was made was 1 to 7. Systematic emphasis on modern diagnostic criteria, including the Wassermann reaction, reduced the ratio, by 1915, to 1 to 4.5. Yet this is far from ideal, and very much short of the possibilities of the new methods. Dudding, and Fildes and Dudding, of the British navy, in criticizing the efficiency of the Royal Naval Medical Service for a ratio of 1 to 4, call attention to the fact that at least 65 per cent of venereal lesions can be diagnosed as syphilitic at once, by the use of the dark-field microscope, provided the lesion has not been tampered with, and that only 14 per cent of those undiagnosed by this means are subsequently shown to be syphilitic by the Wassermann follow-up. If such facts be accepted, and my own impression is that they fall short of little of the truth, there can be no excuse for a higher ratio than 1 to 1, in the comparative diagnosis of primary and secondary syphilis under the conditions of civil life. The newer staining methods, such as those of Medalia, may bring the ratio even lower. There is no real obstacle, either on the score of expense or inaccessibility, to the very wide adoption by the profession of the only significant means of diagnosis for syphilis at a period when its disastrous sequelæ are being in the hollow of our hand.

Though there are many explanations and excuses to offer, let us frankly concede that thus far as a profession we have not had a just conception of the vital importance of early diagnosis in syphilis, or of our responsibility in regard to it. It has taken this war to teach us and the world that modern knowledge of the disease has never been taught in medical schools. Too many experts in it have seemed to choose to devote their energies to the rehabilitation of its wreckage rather than to the more thankless and less remunerative task of its cure in the early days of the chancre. As students we have had hammered into us the unfortunate and misleading clinical characteristics and means of differentiation of the primary lesion. In the dispensary we indulged in old-school arguments over the relative importance of induration, painlessness, multiplicity, etc., forgetting that a tyro can recognize the Hunterian induration, but that mere clinical dialectics will never penetrate the disguise of an infected herpes, a scabetic papule, a benign balanitis, a phimosis, a gonorrhea superimposed on a chancre of the fossa navicularis. Under all these forms an overwhelming amount of syphilis has gained a foothold in the human race. Clinical differentiation of the

nary lesion has gone to scrap, and laboratory diagnosis, the finding of the *Spirochætæ pallida*, is its successor. Not the Wassermann reaction. I hasten to add, for when this becomes positive, the great opportunity is lost. To the recognition of syphilis by identification of the organism, the training and knowledge of a large part of the profession of lay is perhaps inadequate. The more reason then why, in our effort to bring to bear every resource we can muster on this problem for the public good, we should, as we have many times done before, concentrate the energies of specially trained men on this work of early diagnosis of syphilis by the means I have described. How to create such a body of specially trained men in sufficient numbers to have one at hand when the need arises is a master problem in coöperative medical practice, and one for which I shall suggest a solution, after considering the Wassermann reaction in its relation to the problem of diagnosis.

## II. CLINICAL DIAGNOSIS AND THE WASSERMANN REACTION

Medical men of recent vintage, and older men as well, have been rigorously impressed with the vast diagnostic possibilities of the Bordet-Gengou phenomenon as applied to syphilis. There has arisen in our midst a school of dogmatists, the Wassermann negative clinicians, whose yea is yea and whose nay, nay. To them a positive Wassermann may, of course, mean syphilis, but a negative, even a single one, is the final and convincing proof of the absence of the disease. This blind and indiscriminating allegiance to the findings of the laboratory on the part of present-day clinicians is one of the stumbling-blocks in the path of the syphilographer. Misapplications of this sort seem to be the fate of all short-cuts in medicine. Whenever syphilis is a factor, the negative Wassermann is especially an object of unreasoning veneration, because it relieves the examiner of further trouble on a very troublesome score. Our reaction to it is part and parcel of that unfortunate mental inertia, where this disease is concerned, which makes us willing to believe almost anything which will prove its absence, and thus save us the labor and embarrassment which are entailed in demonstrating its presence. No man whose acquaintance with clinical syphilis is intimate foolishly belittles one of our most precious diagnostic aids. Yet every man who works in the midst of syphilis, instead of on its outer fringe, realizes that clinical as distinguished from serologic syphilology is not dead, and that we have yet to return in humility to the feet of the masters who diagnosed brilliantly when Bordet and Wassermann were in their cradles.

This seems a singularly heretical utterance for one who, but a month ago, was clamoring for the laboratory diagnosis of early syphilis, and the apparent discarding of clinical criteria. My contention is that ~~no~~ method of procedure, clinical or laboratory, has its place. The Wassermann has none in the laboratory diagnosis of true primary syphilis. In the florid eruptive secondary stage the reaction is a godsend to the practitioner, hard pressed by the necessity for dermatologic differentiation. In the later periods of the disease clinical differentiation again comes strongly to the front. There is no sadder example of a man ~~gone~~ after strange gods than that of a clinician calling for Wassermann after Wassermann in the frantic effort to get a negative report because the patient with the lesion of the palate or the leg, or the condyloma ~~ad ani~~ happens to be a member of one of "our best families," and high in public life. No man will practise medicine adequately, no man will fit into the place of the profession in the new movement against syphilis, who does not realize the limitation of the negative Wassermann, who does not distrust it enough to know that the palm of the hand, the fundus of the eye, the posterior surface of the scrotum, the border of the tongue, the skin of any part of the body, may present evidence to controvert a thousand negative Wassermans. Such purely clinical evidence, he who reads both may and must read, and interpret. There is awaiting us an era of renaissance in the clinical diagnosis of constitutional syphilis, coincident with a growing appreciation of the fallibility of the negative Wassermann.

If the negative Wassermann is destined to yield, in some degree, to clinical judgment, the positive Wassermann must, in turn, have a restoration to medical confidence. A false positive Wassermann is a diagnostic malfeasance of the gravest type. Better a thousand returns of negative Wassermans in cases otherwise clinically recognizable or suspicious of syphilis, than one return of a positive in the absence of the disease. While it is certainly true that the most expert serologists cannot escape the production of some false positives, it is equally true that frequent false positives are the product of inexperience and over-enthusiasm. The amateur serologist plays with the highly fortified antigens as a baby with dynamite. He approaches his problem with the attitude of a prosecuting attorney, and boasts of his ability to prove a positive. Whatever savors of technical inexperience, of the unjudicial and uncritical temperament, of personal motive and commercial interest, of haste and inaccuracy, has no place in the performance of a reaction

as important as this one. Yet every day we allow such elements to enter into our diagnostic management of syphilis. We shall not measure up to our duty in the new movement against the disease until we shall have done away with the unreliable positive Wassermann so far as human fallibility permits. We shall accomplish this end again by a wholesale pooling of personal, state, and general professional resources. The practitioner who does occasional Wassermans on the side will yield to the great state or hospital laboratory, supervised by a serologist whose personal equation and margin of error are constant and minimal. The commercial advertising laboratory, now uncontrolled, will be done away with or will conduct its activities under a rigorous governmental control, such as that which the United States Public Health service exercises, for example, over the manufacture of biologic products and arsphenamin. With every possible factor of unreliability eliminated from the performance of the reaction, with the negative Wassermann once more subordinated to the clinical evidence of syphilis, and with the identification of the *Spirochæta pallida* by stain or dark field replacing the Wassermann and obsolete clinical criteria in the diagnosis of very early primary lesions, we shall enter upon a new era of efficiency in syphilology.

I venture in leaving the problem of diagnosis to urge upon you the possibilities for usefulness of the heretofore obscure specialty of syphilology. A syphilographer is not a man who knows all about syphilis. You may know the true syphilographer, I hope, more by his diffidence than by his arrogance. His great function is to coördinate a field to which Osler's aphorism justly applies, "Know syphilis in all its manifestations and relations and all other things clinical will be added unto you." The syphilographer is the man who will know what we slangily speak of as the "wrinkle" that helps general men and other specialists out of a tight place in diagnosis. In the new movement against the disease, encourage him. If a man in a town of 10,000 secures a dark field and shows good evidence of special training and aptitude in dealing with syphilis, stand back of him, use him, and help him to enlarge his horizon. Get together, as a medical society, and discuss who, within striking distance of you, does a reliable Wassermann, and then all patronize him and boost his efficiency. Let the local surgeon pause before removing a finger or a limb for "sarcoma," or a primary lesion of the lip or tongue, simulating an epithelioma with glands, or condylomas in the guise of atypical hemorrhoids, until he has called in the man



in his locality who is interested in and has some special knowledge of syphilis. Never let a bubo pass without a glandular aspiration for spirochaetes. Cease to do circumcision in the presence of undiagnosed lesions on the foreskin. Punish with your scorn and medical ostracism the man who uses cauterization, dusting-powder, and pooh-pooh upon the penile sore, or upon the eroded papule or leukoplakial plaque on the mucosa, until he has competent advice on the question of syphilis. A new day will dawn for the social order and for our patients when we are not afraid publicly to denounce as a quack the man to whom all dermatoses are simply "heat rashes" or "ring-worm" or "eczema." It is only by shoulder-to-shoulder coöperative work of this sort that we shall be able to win the degree of public confidence essential to the successful conduct of the new campaign against syphilis.

### III. THE PROBLEM OF MORE EFFICIENT TREATMENT

Our second great obligation as a profession in the movement against syphilis is to provide more efficient treatment. The outstanding difficulties in the present unsatisfactory situation concern: (1) The fact of the high cost and the necessarily long duration of treatment; (2) the difficulty of maintaining the patient's coöperation; (3) the unwillingness of patient and physician to be contented with symptomatic results; and (4) the inroads made by quackery on a field of this character.

*Cost.*—The high cost of treatment for syphilis is a problem whose seriousness no physician has lacked opportunity to appreciate, sometimes to his own cost. The long duration of the disease, the necessity for repeated elaborate tests, the time-consuming manipulations, all make the proper care of a case a burden on the physician quite as much as on the patient. If we are to make effective headway against the disease we must be prepared to put the maximum of effort on its early stages. Yet at this stage of the game the large majority of our patients will be in the least productive period of their lives, just starting to make a way in the world, and not in position to carry a heavy financial burden. When in later years they reappear in the guise of tabetic bank presidents, retired farmers with aortitis, wealthy merchants with hepatic cirrhosis, ready to barter their last possession for a bit of health, nothing can be done. It is indeed a wise provision of the Scandinavian type of public program, after which our own is patterned, which draws on public funds for assistance in treatment when necessary, preferring rather to pay taxes to secure healthy citizenship, than to pay them to support

invalidism. But such plans will not be of immediate or universal application, no matter how ambitious the program for public facilities. There is great need for an immediate concerted effort to reduce the cost of treatment for syphilis for that very large class of patients of moderate means who fall between public charity and the expensive private services of the specialist. This movement has already had some application to other fields of medicine, as you know. A great step in advance in the treatment of syphilis can be made in a short time by the pooling of resources and the treatment of a number of patients under one central direction. Such centralized service for the management of syphilis can be established in connection with the larger hospitals and medical groups at the present time, and is capable of providing both a high-grade treatment and an advisory service for ordinary people at moderate cost. For admission to such a service the patient should pay a minimum advance fee that covers the cost of medication, his professional fee being subject to later adjustment according to his means. If he is not able to meet the advance fee, he should, in general, apply for aid to a public dispensary. Pay services of this type can be carried on economically and yet command a large and very acceptable clientele. The returns, both financial and scientific, justify the time and attention of an expert. In this type of organized effort for the better care of syphilis all the voluntary incentives to the best type of coöperation between physician and patient can be brought to bear. Early diagnosis is available, treatment can be made more nearly ideal, each patient can be followed up and can learn the social and personal relations of the disease. The disastrous effects of being lost sight of during the contagious period and later can be largely prevented. I can unhesitatingly commend to your attention this innovation in the coöperative management of syphilis as an adjunct, and a most necessary one, to the measures contemplated in your public plans for reducing the cost of treatment. You should not wait passively for the state to take over the whole situation, for between the announcement of the program and the completion of the work you will find innumerable difficulties, best met by providing a temporary but effective substitute in private initiative.

*The patient's coöperation.*—Our second obstacle to efficient treatment, the failure of the patient to coöperate, is often as much our responsibility as his. There are undeniably those who will do what is best for them only under duress and legal compulsion. But I have found the large majority of syphilitics to be extraordinarily amenable to the

personal touch, and more often careless or indifferent through ignorance than folly. Few really intelligent human beings—and there are a large proportion of them among the victims of this disease—will deliberately seek their own disadvantage if the matter is laid before them in an understandable yet authoritative manner. We do not need to wait for the promulgation of laws to bring syphilis to book. In fact, if we do wait our very passivity will make the laws dead letters when they come. Each one of us must be active in seeing that the number of patients who disappear from his care uncured is brought to an irreducible minimum. Frankness, fearless honesty, thoroughgoing knowledge, and a warm-hearted humanity on the part of his physician make as strong an appeal to the syphilitic as to any other patient. To supply more of these qualities in ourselves is the best way to meet the reproach that we cannot hold syphilis to adequate treatment.

*Symptomatic cure.*—The common acceptance of symptomatic and partial criteria as standards of cure is the most serious aspect of the problem of more efficient treatment. For one man the symptomatic clue for stopping treatment is the disappearance of the eruption or the healing of the lesion. For another it is the first or the second negative Wassermann. A third will say to his patient, at the end of three years of treatment and Wassermans, "You have had 20 injections of arsphenamin, and five courses of mercury salicylate. I have done all that the best practice requires. You are cured." Within a year the patient will die, as I have known him to, of general paresis. Such cases simply point the moral, that the search for evidence of cure in this disease must extend into every nook and cranny of the body, and employ every conceivable resource. The provocative test, the examination of the fundus of the eye, the condition of the eighth nerve, the spinal-fluid examination, must all be employed, and then the result can only be interpreted in the light of a dull clinical experience with the case. The pitfall of symptomatic results and false cures will never be done away with until each and every one of us realizes that there is no one finding or symptom which signalizes the cure of syphilis, not even reinfection, so long as the question of superinfection is not laid to rest. Neither is there any specific amount or kind of treatment which can be regarded as standard, though the misconceptions on this score are well evidenced by the practitioner's favorite question, "What is your treatment for syphilis?" In the face of the moot points and contentions that confront us everywhere it is impossible to dogmatize. Repeated negative Wassermans

may be obtained (Frühwald) on persons in whose blood the *Spirochæta pallida* can be demonstrated by animal inoculation. Active lesions may appear on the mucosa of patients who are Wassermann negative, or who are in the midst of intensive mercurial treatment with inunctions or insoluble injections. On the one hand, one sees neurorecurrences from the inefficient use of salvarsan; on the other, from the inefficient use of mercury, and again following the adequate and intense administration of both drugs. We see a woman at the age of forty-five, with nothing remaining of her infection except a low-grade choroiditis and a reduced bone conduction with normal hearing. Treatment in her case had consisted of a few weeks of pills during her eruptive period. Her husband, after receiving essentially the same treatment, is now an advanced case of paresis. A given patient has, by painstaking and persistent use of modern methods, been gradually freed from all clinical and serologic signs of the disease and has remained free. To compare with him we have another patient of seemingly the same type, who, under the same management, has obstinately refused to respond. For the confusion of mind which the contemplation of these things engenders I can only offer certain generalizations to guide you in your use of modern methods in the treatment of syphilis.

Accept no single sign of improvement in the disease as an indication to stop treatment if the tolerance is normal. Only the all-around cessation of the process means anything, and it means nothing unless it persists through months and years.

Arsphenamin therapy is essential. It, and not mercury, controls contagiousness. It, rather than mercury, yields the quick symptomatic result.

Mercury is indispensable—a homely but reliable servant, the basic factor in permanence and the great renewer of immunity.

Most syphilis is undertreated. Strike hammer blows and strike them early. Treat a little too much rather than not enough.

Promise no man a cure, and release no patient from the obligation of occasional observation throughout life. Our experience with modern methods is still too brief to justify anything but an extreme conservatism. The man who treats syphilis with these principles in mind will be an efficient servant of the public good in whatever capacity he may be called.

*Fraudulent exploitation.*—Few physicians, I think, realize their full duty toward quackery and fraudulent exploitation in the field of the

Their return will be followed by a wholesale dissemination of knowledge at second hand which will penetrate every corner of the earth. It will compel a revision of medical standards, which we can do no less than anticipate voluntarily. Where will the man be who says, "I do not believe in the *Spirochæta pallida* and salvarsan," five years from now? Traditional silence, ultraconservatism, and stand-pat ethics will be swept to oblivion, and their adherents with them. Already Italy and Germany have inaugurated, in a most uncompromising fashion, a campaign of public enlightenment which we Anglo-Saxons are perhaps disposed to regard as extreme. Dissemination of knowledge on venereal prophylaxis and treatment to the population at large has the sanction of these governments, and its spokesmen are like Blaschko and Stannick among the leaders of the medical profession in the field in their respective countries. If we sit by while public understanding of the situation strips us and goes on to the development of new policies in which we have been obstructionists rather than participants and leaders, spokesmen and molders of public opinion, we shall richly deserve the contempt which will be ours. There cannot be too much enlightenment, and the responsibility for its authenticity, its high moral quality, and its universal spread is up to us. If we let the ministry stand sponsor for the moral laymen for the authenticity, and the Y.M.C.A. for the enthusiasm, shall we not stand justly accused of what Robert Louis Stevenson prayed to be delivered from—cowardly silence and misleading speech?

What shall we do? First, be informed on the situation. Every physician should be vitally interested at this time in the whole movement for the control of venereal disease in the armies and navies of the world. We should be reading the literature, studying the returns, asking questions. From the efforts of medical officers particularly we must draw the lessons which will enable us to control the situation in civil life. Civil life is the focus of infection. Contrary to the usual conception, there seems little reason to doubt that the percentage of venereal infection is much higher in the general population than it is in the military forces of the world. This brings the obligation for the deplorable conditions which have prevailed squarely on us. The well-known increase in venereal morbidity occurring during the mobilization of troops illustrates the immediacy of the relation. With all due allowances made for the somewhat greater disposition to sexual laxity among recruits which prevails at such a time, we cannot fail to be impressed with the index of civil conditions furnished by the flood of venereal infection which

occurs coincidentally with each new increment to an army from the general population. No one army or nation has a monopoly of this situation. The Surgeon General's reports for the United States armies during the various mobilization movements are perhaps the best body of statistics extant illustrating the point, though the observations of Klausner, Tullidge, Thibierge, and others have shown that high mobilization rates have been the rule the world over, and that they have been in the past too little appreciated, owing to the lack of adequate statistics covering the point (Great Britain, for example). There can be no escaping the fact that unless we make the most heroic efforts to control the sources of infection in civil life, the work of our army surgeons will be nullified repeatedly by the wholesale importation of infected material and by the constant exposure of the personnel to risks, which even the most rigorous prophylaxis cannot minimize.

Physicians have, I think, in the past, been entirely too prone to separate social from medical problems, and to appropriate the latter to themselves, leaving the former to a stepmotherly care at the hands of laymen. Such an attitude spells retrogression in the control of venereal diseases. If there is any field in which the physician can appropriately play the rôle of sanitarian, moralist, clergyman, lawyer, and business man, it is in this one. One of the revelations of the war has been the importance of the personal, the social, and the moral factors in the control of disease in general, and of venereal disease in particular. Athletic activities, recreation, letters from home, the theater, hot coffee, have all been called on to help in the maintenance of morale. Lessons of direct applicability to the civil population are to be learned on all sides from the success of the American Commission on Training Camp Activities, the International Y.M.C.A., the Committee on Civilian Coöperation of the Council of National Defense, the Salvation Army, and similar types of organization of the various belligerent countries, whose task has been to keep the soldier "Fit to Fight." We believe that the United States, at the outset of its participation in the war, set an example worthy of your emulation, in standing for the outright suppression of prostitution wherever it can be reached, rather than its official toleration, as in Germany and France, its actual officialization as in Italy and Japan, or the attitude of *laissez faire* which even British officers have been obliged to confess has marred their army program. From our armies we must draw the lessons in ideals and methods that will enable us to cope with our side of the problem in the general population. That part of the

profession which still holds the outposts in civil life in all parts of world cannot ignore its opportunity and its duty. Every town with furlough distance of a cantonment which contains a vicious rendezvous for soldiers means a slack medical profession, quite as much as an inefficient police force and a low morale. Every medical examiner who certifies a man to be physically fit, without at the same time warning him in brief but unmistakable terms as to how he should preserve his fitness, has lost an opportunity to serve in the first-line trenches in this fight. Every woman known to be a source of infection who continues to ply the trade is a reflection on some one of us who has not done his best to suppress such activities. The batches of infected men who go to the bilization camps are less a stigma on the civil population at large than on its physicians who know what these things mean, and have tolerated them. No law except our consciences can exact of us these vital sacrifices to our cause. Let us see that they pledge us to them without reservation.

I think that medical men generally are also too much inclined to take negative attitudes on social questions. We must have only one ideal in this work—to emulate the apostle in becoming doers of the word and not hearers only. These are the times for us to cast dignity aside and throw our hats into the ring. See that there is a brick in each hat and the man that kicks it. Be positivists. Stand for no less a principle than the absolute suppression of every vicious incentive to sexual activity. Preach continence without a smirk. See that no man is victimized through ignorance of the situation. Never let medical prophylactic advice to the man who exposes himself be your last word on the subject. Most of us have sons. Most of us know what it will mean to us to see them grow into straight men, men of honor and integrity, with unbesmirched bodies and minds. How can we contemplate with equanimity the line-up of our sons before a row of official prostitute or offer to the boy who represents our immortality and our hope a tube of calomel ointment with the satyric injunction, "if you can't be good be careful." There is still enough worth while in clean living to commend the support of red-blooded men. Nor could there be a more pitiful commentary on the anemic quality of our moral fiber than to have the social hygiene of the future become the plaything of faddists, and the "unco guid" the rallying ground of cranks and prudes.

Let us, then, use every opportunity to mold legislation, to teach, and, if the opportunity offers, to preach. Sooner or later Canada:

physicians, no less than those in every other country, will confront the problem of the dissemination of prophylactic knowledge on venereal disease among the public at large. Begin to give the matter earnest thought, and to educate public sentiment to its dangers as well as its advantages. Medical prophylaxis for venereal diseases should, I believe, remain under the control of the profession, and it will be one of our first duties, after being able to administer it, to see that it is never given without a generous and effective dose of moral and educational prophylaxis. It is one of the specific provisions of the military medical code of the United States army that the prophylaxis shall never be permitted to become a laughing matter, and that it shall be in the hands of men whose prestige and responsibility fit them to say the effective word or two that keeps many a young fellow from becoming a "repeater." Prophylaxis is too effective an instrument against venereal disease to long remain in the background when the campaign is once in full swing. See to it that it is effective for good and not for evil when the power to use it is placed in your hands.

Let me urge it on you that you teach. If more of you would appreciate the *ex cathedra* position which the medical profession holds on the subject of venereal diseases, you would teach for the sheer delight of being heard as gospel. Let those among you with the compelling eye and the power to swing the vernacular use those powers in behalf of public enlightenment, and let stutterers discretely hold their peace. Much able work has been done by committees of medical societies and boards of health in the United States and in our larger cities in the development of organized intelligent publicity on the subject of venereal disease prevention and control. One of the most effective methods thus far found has been the use of visual impressions, always the most vivid and convincing mode of teaching, in the form of so-called health exhibits. In these exhibits, authentic information is conveyed by placards and picture posters, skilfully prepared. Such exhibits can be obtained from the American Social Hygiene Association in New York, and set up in small towns and concentration camps, hospitals and Y.M.C.A. centers. They are immeasurably superior to tracts and leaflets in teaching the average layman, as the experience of the armies abroad has shown. None of this work is too petty for us to do, and all of it yields a substantial return in the more intelligent coöperation which it gains for us on all sides.

I realize that I have been talking to busy men, hard pressed by the





# THE ETIOLOGY OF EPIDEMIC POLIOMYELITIS\*

E. C. ROSENOW AND G. W. WHEELER†

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A somewhat peculiar diplococcus or streptococcus has been found in the spinal fluid and in the brain and cord of cases of poliomyelitis by various observers. In some instances injections in animals gave suggestive although inconclusive results indicating the causal relationship of this organism. Other workers were unable to obtain corroborative evidence. Efforts to demonstrate bacteria in sections proved unsuccessful. The discovery that typical poliomyelitis can be produced in the monkey with so-called virus and filtrates of virus,<sup>4, 9, 10</sup> and the successful inoculation of monkeys by Flexner and Noguchi with the small "globoid" organism which they cultivated from the central nervous system in poliomyelitis, was considered final in proving that bacteria of ordinary size had no etiologic relation to this disease. The status of the question of the relation of these organisms, particularly streptococci, to poliomyelitis, when we began our studies is tersely stated by Wickman: "Such bacteria must be regarded as having had an accidental and not a causal relation to the malady."

However, since the earlier studies were made, special methods have been developed and bacteria of ordinary size have been isolated from tissues which were considered sterile. The localization of these bacteria in animals frequently corresponded closely to that in the disease from which they were isolated. In view of these results the older investigations were considered inconclusive as proving that bacteria of ordinary size had no etiologic relationship to poliomyelitis, and a restudy of the bacteriology of poliomyelitis by the use of the newer methods was undertaken.

We wish now to record the details of a study of a series of cases of poliomyelitis which occurred in Rochester, Minnesota, and New York City during the epidemic of 1916, and in Davenport, Iowa, in 1917.

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The results of the cases occurring in 1916 have been described in a preliminary report<sup>19</sup> in which the following statement was made:

"It appears to us that the small, filtrable organism which has been generally accepted as the cause of poliomyelitis may be the form which this streptococcus tends to take under anaërobic conditions in the central nervous system and in suitable culture-mediums, while the larger and more typically streptococcic form, which investigators have considered contaminations, may be the identical organism grown larger under suitable conditions."

#### RESULT OF A STUDY OF CASES WHICH CAME TO NECROPSY

In Table 1 is given a summary of the clinical, pathologic, and bacteriologic findings of 19 cases of acute poliomyelitis in which necropsies were done.\* The ages of the patients ranged from seven months to twenty-four years; only 5 were more than six years. The duration of symptoms was from one to fifteen days. The extent of flaccid paralysis varied greatly in the different cases. Nearly all these patients died of paralysis of the muscles of respiration. Bronchopneumonia was found in 4; a terminal rise in temperature suggesting antemortem infection occurred in 8 of the cases, but was absent in the others. The necropsies were all done within twenty-four hours after death—one in one-half hour, one in one and one-half hours, two within two hours, and seven within twelve hours.

The gross and microscopic findings in all were typical of acute poliomyelitis. The viscera usually showed no gross changes other than congestion and cloudy swelling. The mesenteric lymph-glands were swollen in most of the cases. Peyer's patches were swollen, and the lymphoid follicles in the intestines and mesenteric glands were edematous and hemorrhagic in cases in which there were marked gastro-intestinal symptoms. Localized hemorrhages in the mucous membrane of the stomach had also occurred in a number of the cases. As a routine, portions of tissues were immediately placed in 10 per cent formalin and in some instances in Kaiserling's fluid, for microscopic study. They were embedded in paraffin, and sections from 5 to 10 microns thick were stained with hematoxylin and eosin, methylene-blue and eosin, and with eosin and polychrome methylene-blue, for microscopic study.

The microscopic changes in the brain and cord were typical of polio-

\* The material from nine cases was obtained through the courtesy of Drs. Anna Williams and H. L. Abramson, of the Health Department of New York City.

No.	AGE IN YEARS*	DURATION IN DAYS	CLINICAL FINDINGS	NECROSCOPIC TIME AFTER DEATH	MICROSCOPIC CHANGES	BACTERIA IN SECTIONS	RESULTS IN CULICIDAE
707	4½	7	Paralysis of muscles of left side of face, neck, and deglutition. Death from respiratory failure.	Day of death	Hemorrhage, moderate perivascular and disseminated round-cell infiltration, chiefly in anterior horns and in pia over anterior aspect of cord and medulla.	Large and small cocci and diplococci in pia of anterior flange and anterior aspect of cord, in infiltrated areas in anterior horns of cervical cord and medulla (Fig. 45).	Micrococci and short-chained streptococci varying greatly in size and shape from cord. Diptheroid-like bacilli in old cultures. Streptococcus from brain and cord after three and fifteen months in 80 per cent glycerin.
712	4	5	Paralysis of lower extremities, right shoulder, and death from respiratory failure.	8 hours	Extreme perivascular and diffuse infiltration, chiefly of gray matter of cord and medulla. Perivascular infiltration most marked around vessels. Extending horizontally from pia. Moderate infiltration of pia especially around blood-vessels and in anterior flange. Pyoperia and necrosis of lymphoid follicles in tonsils (Fig. 457). Hemorrhages in mucous membrane of stomach. Small areas of necrosis with round-cell accumulations in liver. Viscera normal otherwise.	Large and small diplococci, at least 40 in all, in infiltrated area anterior horns (Fig. 3), in periphery of anterior flange and anterior aspect of cord, in infiltrated areas in anterior horns of cervical cord and medulla (Fig. 45).	Extremely pleomorphic coccus singly in two and short chains from cord. Spleen, kidney, and liver sterile. Streptococcus and colon bacillus from lumbar cord.
714	2	15	Paralysis of legs and shoulders. Death from respiratory failure.	4 hours	Cord showed extreme dilatation of vessels, hemorrhages, marked degeneration of ganglion-cells; slight neurophagia; moderate perivascular infiltration with round cells. Slight infiltration in ganglia. No leucocytes in liver, myocardium, pancreas, kidney, and spleen. Hemorrhages and leukocytic infiltration of lung. Marked hyperplasia of lymphoid follicles in tonsils. Slight perivascular, moderate infiltration of gray matter of cervical cord with destruction of ganglion-cells. No changes in secondary changes in spinal cord.	Large and small diplococci in areas of hemorrhage and infiltration in anterior horns, in contact, films from cerebellum (Fig. 454). Many similar organisms in tonsils and diplococci in hemorrhagic area in lungs. No bacteria in liver, kidney, spleen, myocardium, and pancreas.	Streptococcus from edematous fluid surrounding dura, from cerebral fluid, brain, lumbar cord, and from brain after being dried from six to eleven months respectively. Kidney sterile. Streptococcus in pure culture from brain and cord after being in 80 per cent glycerin three, eight, fifteen, and sixteen months.
720	3	3	Paralysis characteristic of upper spinal type.	20 hours	Typical polymorphic changes in spinal cord. Numerous changes in viscera other than localized hemorrhages and leukocytic infiltration of lungs. Perivascular infiltration most marked around blood-vessels running in pia; extensive areas of round-cell infiltration with destruction of ganglion-cells in cord. No changes demonstrable in brain. Areas of necrosis of lymphoid follicles in tonsils. Liver, pancreas, and myocardium normal.	Diplococci in anterior horn of cervical cord and intervertebral ganglia. No bacteria in liver, lung, and pancreas.	Short-chained diplococcus from cervical cord and brain.
721	9/12	6	Paralysis of meningitic type.	Day after death	Typical polymorphic changes in spinal cord. Numerous changes in viscera other than localized hemorrhages and leukocytic infiltration of lungs. Perivascular infiltration most marked around blood-vessels running in pia; extensive areas of round-cell infiltration with destruction of ganglion-cells in cord. No changes demonstrable in brain. Areas of necrosis of lymphoid follicles in tonsils. Liver, pancreas, and myocardium normal.	A few cocci and diplococci in peripheral zone of round-cell infiltration in anterior horns. Many similar organisms in tonsils. Diplococci in liver and kidney areas in lungs. No bacteria in liver and kidney areas in lungs. A few large and rod-shaped diplococci in peripheral zone and rod-shaped diplococci in matter of medulla and cerebellum. A few cocci and diplococci in hemorrhagic areas in meningeal glands. Extensive necrosis of anterior horn in periphery of lymphoid follicles of tonsils together with fusiform bacilli in crypts of tonsil. No bacteria in brain, liver, pancreas, myocardium.	Short-chained streptococci and large and small cocci from cervical cord and brain. Hemolytic streptococcus and rod-shaped bacilli from cord. Streptococcus and large and small cocci from pure culture from material obtained from paper from brain and cord, and streptococcus and a few diplococci from pieces of cord embedded in mortar, and from mesenteric gland.
722	3	4	Paralysis of upper spinal type.	Day of death	Typical polymorphic changes in spinal cord. Numerous changes in viscera other than localized hemorrhages and leukocytic infiltration of lungs. Perivascular infiltration most marked around blood-vessels running in pia; extensive areas of round-cell infiltration with destruction of ganglion-cells in cord. No changes demonstrable in brain. Areas of necrosis of lymphoid follicles in tonsils. Liver, pancreas, and myocardium normal.	A few cocci and diplococci in peripheral zone of round-cell infiltration in anterior horns. Many similar organisms in tonsils. Diplococci in liver and kidney areas in lungs. No bacteria in liver and kidney areas in lungs. A few large and rod-shaped diplococci in peripheral zone and rod-shaped diplococci in matter of medulla and cerebellum. A few cocci and diplococci in hemorrhagic areas in meningeal glands. Extensive necrosis of anterior horn in periphery of lymphoid follicles of tonsils together with fusiform bacilli in crypts of tonsil. No bacteria in brain, liver, pancreas, myocardium.	Short-chained diplococcus from cervical cord and brain.

TABLE 1.—RESULTS OF A STUDY OF CASES OF ACUTE EPIDEMIC POLIOMYELITIS—(Continued)

No.	AGE IN YEARS	DURATION IN DAYS	CLINICAL FINDINGS	NECROPSY TIME AFTER DEATH	MICROSCOPIC CHANGES	BACTERIA IN SECTIONS	RESULTS IN CULTURES
723	34	6	Paralysis of right deltoid, right and left quadriceps and psoas muscles of deglutition and diaphragm.	2 hours	Slight round-cell infiltration in pia over cerebrum. Areas of necrosis in lymphoid follicles in tonsils. Hemorrhages in mesenteric gland. No changes in liver, pancreas, myocardium, or kidney.	No bacteria demonstrable in brain. Large number of large and small cocci and diplococci in necrotic lymphoid follicles in tonsils. Many large forms breaking into small forms. A few large and small diplococci in hemorrhagic mesenteric gland. No bacteria in liver, pancreas, myocardium, or kidney.	Pleomorphic streptococcus from ventricular fluid, cerebrum, medulla, and cervical cord, and diphtheroid-like bacillus from brain.
724	1½	3	Paralysis of muscles of neck and left side of face. Death from respiratory failure.	12 hours	Brain and cord not saved for microscopic examination.	A few diplococci in cord. No bacteria in myocardium.	Large and small streptococcus from brain, pons, and cervical cord, and Gram-negative bacillus resembling colon bacillus from brain.
725	1½	4	Paralysis of both legs, back, shoulders, and intercostal muscles. Death from respiratory failure.	22 hours	Typical poliomyelitic lesions in cord and brain.		Medium-sized streptococcus and large and small diplococcus from cerebrum, pons, and cervical cord.
729	3	9	Paralysis of right side of face, muscles of neck, upper extremities, and intercostal muscles. Death from respiratory failure.	3 hours	Extreme diffuse round-cell infiltration and numerous hemorrhages in gray matter of cervical cord and medulla. Moderate perivascular infiltration of column, and slight infiltration of pia, of cerebral cortex and spinal ganglia. Congestion of vessels of liver and kidneys. Hyperemia and hyperplasia of lymphoid follicles in mesenteric gland. Otherwise no noteworthy changes in viscera.	Large and small diplococci in edematous capsule of spinal ganglia, in pia over anterior aspect of cord, in leukocyte in anterior horn, in pons, in edematous areas surrounding infiltrated blood-vessels, in mesenteric gland, and in contact blue from cerebrum (Fig. 245). No bacteria in sections of brain, liver, heart, tonsils, or kidney. Diplococci in areas of infiltration in sections of cord after in glycerin for fifteen months. Many organisms exactly the same as necrotic follicles of tonsils.	Pleomorphic streptococcus from blood, spinal fluid, cerebrum, pons, cervical cord, and mesenteric gland. No bacteria in kidney, liver, or spleen. Colon bacillus from lumbar cord and mesenteric lymph-gland. Streptococcus and large coccus forms from brain and cord after in 50 per cent glycerin for fifteen months.
734	1½	6	Typical ascending paralysis.	Day after death	Marked hemorrhages and diffuse infiltration in anterior horns of cervical cord. No changes in brain.	A few diplococci in areas of hemorrhage in cervical cord. No bacteria in brain.	Streptococcus and large diplococcus from brain and cord after in 50 per cent glycerin for fifteen months.
749	5½	5	Paralysis of muscles of deglutition and left side of face. Death from respiratory failure.	15 hours	Moderate perivascular and slight diffuse infiltration and numerous hemorrhages in gray matter of medulla and cervical cord. Hemorrhages in mesenteric gland. Small areas of necrosis in liver, spleen, and kidney.	Large and small diplococci in hemorrhagic areas of medulla. Small diplococci and chains of two in sections of anterior horns in smears from epidural of cord (Fig. 250) and in smears from cord after in glycerin for fifteen months. Many smaller diplococci in necrotic areas in tonsils and medulla.	Pleomorphic streptococcus from cerebrum, pons, and cervical cord. Streptococcus and large coccus forms from brain and cord after in 50 per cent glycerin for two and fifteen months respectively
778	9	15	Paralysis of extremities, muscles of deglutition. Death from respiratory failure.	2 hours	Moderate perivascular and circumferential infiltration in anterior horns and pia and in white matter of posterior horns and pons. No changes in viscera.	A few large and small diplococci in pia and infiltrated areas in cord.	

779	2	3	4	5	6
936	12	5	Brought to hospital in moribund condition. Death from respiratory failure.	1 1/2 hours	<p>Extensive perivascular infiltration in gray matter of cord and brain. Many hemorrhages, chiefly in anterior horns. Many of the infiltrating cells are polymorphonuclear leukocytes. Extreme diffuse and perivascular infiltration in anterior horn of cord, in medulla and pons; slight in brain.</p> <p>Hemorrhage and leukocytes in alveoli of lung. Hemorrhage in mesenteric lymph-gland. Small areas of round-cell infiltration in liver. Localized areas of leukocytic infiltration and hemorrhage in lung. No lesions of other viscera.</p> <p>Extreme round-cell infiltration, diffuse, cord and perivascular in anterior horns of cord and moderate in rest of brain. Many of infiltrating cells are polymorphonuclear leukocytes. Extreme hyperemia and hemorrhage in mesenteric gland. Focal necrosis of liver with round-cell infiltration. Leukocytic infiltration in lung. No changes in myocardium, kidney, or spleen.</p> <p>Marked round-cell infiltration of gray matter of cord; perivascular infiltration and areas of hemorrhage. Areas of necrosis in lymph-follicles of tonsil. Hemorrhage and hyperplasia of mesenteric lymph-glands. Focal necrosis in liver. No change in kidney or myocardium.</p> <p>Extreme perivascular and diffuse infiltration with round-cells in gray matter of medulla. Slight in pons and brain. Areas of hemorrhage and glomerulonephritis. Areas of necrosis of lymph-follicles in tonsils.</p> <p>Necrosis in lymphoid follicles of tonsils and adenoids. Hemorrhage of mucosa and submucosa of stomach, perigastric and mesenteric lymph-glands.</p>
943	2	1	Paralysis of left side of face, muscles of left leg, and thorax. Death from respiratory failure.	3 hours	<p>Large and small diplococci in edematous areas around infiltrated blood-vessels and infiltrated areas in medulla and lumbar cord and in mesenteric gland. Very many similar organisms in necrotic areas in lymph-follicles of tonsils. No bacteria in stomach, kidney, liver, or spleen. A few diplococci in pneumonic areas in lung.</p> <p>Very large and medium coccus and diplococcus forms in medulla, pia over cerebrum. Many similar organisms in areas of necrosis in follicles of tonsils. A few in hemorrhagic areas in stomach. No bacteria in kidney, myocardium, pancreas, intestine, or lung.</p>
948	11	4	Paralysis of right side of face, muscles of neck, and thorax. Death from respiratory failure	5 hours	<p>A few diplococci in infiltrated area of anterior horn of cervical cord. Many similar organisms in tonsils. No bacteria in brain, myocardium, lungs, peribronchial lymph-gland, mesenteric lymph-gland, or Peyer's patches.</p>
949	17	3	Paralysis of legs, muscles of abdomen, back, upper extremities, of deglutition and diaphragm. Death from respiratory failure	1/2 hour	<p>Diplococci and chain of two diplococci in pia and anterior horn and in sinners from beneath dura of cord after preservation in glycerin (Fig. 426). Large number of coccus forms, singly in two and short chains in lymph-follicles of tonsils.</p> <p>Enormous numbers of large, medium-sized, and very small diplococci in lymphoid follicles of tonsils, adenoids, and in lymph-channels between muscle-fibers outside of tonsil. Moderate number in hemorrhagic areas in mucous membrane of stomach and a few in mesenteric glands and lymphoid follicles of Peyer's patches.</p>
960	16	3	Paralysis of muscles of deglutition. Death from respiratory failure.	8 hours	<p>Streptococcus and coccus forms from brain, pons, medulla, cervical and lumbar cord, and mesenteric gland. Colon bacillus from pons, lumbar cord, mesenteric gland. Kidney and liver sterile.</p> <p>Streptococcus and large coccus forms from brain, pons, lumbar cord, and mesenteric lymph-gland. Later also showed colon bacillus. Liver and spleen sterile. Large diplococcus in short chains and tetrad from brain and cord after in 50 per cent glycerin for three and one-half and four and one-half months.</p> <p>Pleomorphic streptococcus from brain. Streptococcus and large coccus forms from brain and cord after in 50 per cent glycerin for three and one-half and four and one-half months.</p> <p>Large and small coccus forms sometimes in short chains from brain, medulla, and cervical cord. Streptococcus and large coccus forms from brain and cord after in 50 per cent glycerin for three and one-half and four and one-half months.</p>

TABLE 1.—RESULTS OF A STUDY OF CASES OF ACUTE EPIDEMIC POLIOMYELITIS—(Continued)

No.	AGE IN YEARS	DURA- TION IN DAYS	CLINICAL FINDINGS	NECROPSY TIME AFTER DEATH	MICROSCOPIC CHANGES	BACTERIA IN SECTIONS	RESULTS IN CULTURES
743	24	6	Paralysis of right deltoid, right and left quadriceps and psoas, muscles of deglutition and diaphragm.	2 hours	Slight round-cell infiltration in pia over cerebrum. Areas of necrosis in lymph-follicles in tonsils. Hemorrhages in mesenteric gland. No changes in liver, pancreas, myocardium, or kidney.	No bacteria demonstrable in brain. Large number of large and small roset and diplocoeci in necrotic lymph-follicles in tonsils. Many large forms breaking into small forms. A few large and small diplocoeci in hemorrhagic mesenteric gland. No bacteria in liver, pancreas, myocardium, or kidney.	Plasmorphic streptococcus from ventricular fluid, cerebrum, medulla, and cervical cord, and diptheroid-like bacillus from brain.
744	1½	3	Paralysis of muscles of neck and left side of face. Death from respiratory failure.	12 hours	Brain and cord not saved for microscopic examination.		Large and small streptococcus from brain, pons, and cervical cord, and Gram-negative bacillus resembling colon bacillus from brain.
745	1½	4	Paralysis of both legs, back, shoulders, and intercostal muscles. Death from respiratory failure.	22 hours	Typical poliomyelitic lesions in cord and brain.	A few diplocoeci in cord. No bacteria in myocardium.	Medium-sized streptococcus and large pons, and cervical cord.
746	3	9	Paralysis of right side of face, muscles of neck, upper extremities, and intercostal muscles. Death from respiratory failure.	3 hours	Extreme diffuse round-cell infiltration and numerous hemorrhages in gray matter of cervical cord and medulla. Moderate perivascular infiltration of pons, edema, and slight infiltration of pia, of cerebral cortex and spinal ganglions. Congestion of vessels of liver and kidney. Hyperemia in mesenteric gland. Lymph-follicles in mesenteric gland. Otherwise no noteworthy changes in viscera.	Large and small diplocoeci in edematous capsule of spinal ganglions, in pia over anterior aspect of roset, in leukocyte in anterior horn, in pons, in stemmatic areas surrounding infiltrated blood-vessels, in mesenteric gland, and in outlier flaps from cerebrum (Fig. 435). No bacteria in sections of brain, liver, heart muscle, or kidney. Diplocoeci in areas of infiltration in sections of cord after to glycerin for fifteen months. Many organisms exactly the same as necrotic follicles of tonsils.	Plasmorphic streptococcus from blood, spinal fluid, cerebrum, pons, cervical cord, and mesenteric gland. No bacteria in kidney, liver, or spleen. Colon bacillus from lumbar cord and mesenteric lymph-gland. Streptococcus and large coccus forms from brain and cord after in 50 per cent glycerin for fifteen months.
754	1½	6	Typical ascending paralysis.	Day after death	Marked hemorrhages and diffuse infiltration in anterior horns of cervical cord. No changes in brain.	A few diplocoeci in areas of hemorrhage in cervical cord. No bacteria in brain.	Streptococcus and large diplocoeci from brain and cord after in 50 per cent glycerin for fifteen months.
745	5½	5	Paralysis of muscles of deglutition and left side of face. Death from respiratory failure.	15 hours	Moderate perivascular and slight diffuse infiltration and numerous hemorrhages in gray matter of medulla and cervical cord. Hemorrhages in mesenteric gland. Small areas of necrosis in liver. No changes in lung, pancreas, myocardium, and kidney.	Large and small diplocoeci in hemorrhagic areas of medulla. Small diplocoeci and chain of two in sections of anterior horns in aneurysm from emulsions of cord (Fig. 436 b) and in aneurysm from cord after in glycerin for fifteen months. Many similar diplocoeci in necrotic areas in lymph-follicles of tonsils.	Plasmorphic streptococcus from cerebrum, pons, and cervical cord. Streptococcus and large coccus forms from brain and cord after in 50 per cent glycerin for two and fifteen months respectively
774	2	15	Paralysis of extremities. Death from respiratory failure.	8 hours	Moderate perivascular and circumferential areas of round cell infiltration. Slight perivascular infiltration and hemorrhage in viscera.	A few large and small diplocoeci in pia and infiltrated areas in cord	

were found within cells. They varied greatly in size, shape, and grouping in different locations in the same case, but were much alike in the different cases and occurred in widely separated regions. The variations in size were noted even among the minute forms and when arranged in short chains (Fig. 254, *b*). The very small forms often occurred in groups commonly containing 4 or 8 and sometimes 16 minute cocci, usually in pairs, suggesting the rapid breaking up of large coccus forms into the small forms (Figs. 251, *c*, 255, *b*, and 256, *a*). The very large coccus or diplococcus forms usually occurred along blood-vessels or capillaries.

#### CULTURES FROM THE TISSUES

The cultures were made essentially according to the methods used by one of us in a study of the bacteriology of tissues from various diseases,<sup>15</sup> and that used by Flexner and Noguchi. To obtain the initial growth three mediums were regularly used: (1) Ascites-dextrose broth and dextrose broth in tall (12 cm.) and short (8 cm.) tubes and bottles, with or without sterile tissue; (2) ascites-dextrose-agar and dextrose-agar, usually without tissue, and (3) tall tubes of unheated ascitic fluid plus sterile tissue and oil. The dextrose broth and agar were prepared with Witte's peptone and Liebig's extract of beef, titrated to 0.6–0.8 acid to phenolphthalein. The broth contained 0.2 per cent dextrose, the agar 1 per cent dextrose, and 1.5 per cent agar. The ascites fluid was of high specific gravity, was free from bile, and was previously proved sterile by making aërobic and anaërobic cultures from the sediment of lots of approximately 200 c.c. each. Pieces of brain, medulla, cervical cord, etc., were removed with sterile precautions and emulsified in a sterile air-chamber or fragments planted directly. In some instances pipeted material from the anterior horns or the brain, after searing the surface, were also cultured. Usually a large number of tubes were inoculated with varying amounts of emulsions. Approximately 1 c.c. of a 10 per cent emulsion in normal salt solution per 10 c.c. of medium gave the best results. Both too little and too much emulsion per cubic centimeter might lead to negative results. The cultures were incubated at 35° C. Only a few were put in the anaërobic jar, as it was thought desirable to make frequent smears of all cultures which grew.

Cultures were made from different parts of the central nervous system, usually of spinal or ventricular fluid, brain, pons, medulla, edematous dura, ganglions, and from different levels of the cord. A Gram-staining coccus varying greatly in size, shape, and grouping, but



usually essentially streptococcal in character, has been isolated in 15 of 15 cases. In 8 of the strains chain formation was relatively marked and in 7 it was relatively slight. In most instances the emulsions of the specimens cultured yielded this organism, but not in all the tubes inoculated. The spinal-fluid cultures remained sterile except in two instances, and these showed the characteristic streptococcus. Colon bacilli were obtained usually in only one or more fragments or tubes from 6 cases, hemolytic streptococcus in one instance, diphtheria bacilli in two, and in a few instances *Bacillus subtilis* and *Staphylococcus albus*.

Cultures of emulsions of brain and cord after preservation in 50 per cent glycerol in the ice-chest for from three to sixteen months have yielded microorganisms identical to the one isolated from the fresh tissues in all but 2 of 16 sets of cultures which were made from material from 8 cases.

Cultures from mesenteric lymph-glands were made in 4 cases. All yielded the characteristic microorganism, and in 2 colon bacilli were obtained in addition. The streptococcus isolated constantly from the central nervous system was not found in a single instance in other organs cultured in 5 cases. This result does not bear out the opinion expressed by Kolmer and Freese, that this organism was probably present in these organs, but adds materially to the significance of their complement-fixation tests with antigens prepared from these strains.

The cultures in the short tubes of dextrose broth and bottles showed usually a diffuse granular turbidity in from twenty-four to forty-eight hours. Those inoculated with emulsions grew more often than those inoculated with fragments. Smears at this time showed cocci and diplococci often in short chains and occasionally in long chains of uniform size or, more often, of very irregular size. Subcultures on blood-agar plates at this time gave a growth of small, dry, green-producing colonies which might be surrounded by a narrow, hazy zone of hemolysis, especially after forty-eight to seventy-two hours' incubation. In old cultures in the short tubes of ascites-dextrose broth, and, with few exceptions, in tall tubes containing this medium, the organisms become Gram-negative as they die, but do not grow to small size (Figs. 261.a and 262.a). In shake cultures of the emulsion in short tubes of ascites-dextrose-agar small, discrete, grayish colonies, always in small numbers, appeared in the deeper portion of the medium, never above 1.5 cm. from the top, usually on the second or third day. The cultures in ascites

Fig. 253.—Microorganisms in cervical cord (Case 712) shown in Fig. 252. Gram-Weigert. ( $\times 1000$ .) *a*, Large diplococcus adjacent to blood-vessel at *a*. *b*, Medium small diplococcus, round cells, and leukocytes at periphery of area of infiltration at *b*. *c*, Medium-sized diplococci in pia. *d*, Medium-sized diplococcus in ganglion at *d*.



Fig. 253.

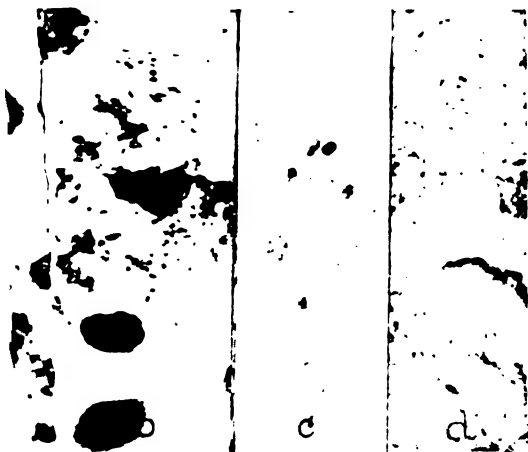


Fig. 254.

Fig. 256.—Microorganisms in nervous system in cases of poliomyelitis. ( $\times 1000$ .) *a*, Group of small, lightly stained diplococci in infiltrated area surrounding blood-vessel, Case 779. Gram-Weigert. *b*, Diplococci in normal salt solution emulsion of cervical cord, Case 745. Gram-Weigert. *c*, Chain of three diplococci in smear from beneath dura of cord of Case 949 after preservation in glycerol for four months. Giemsa.

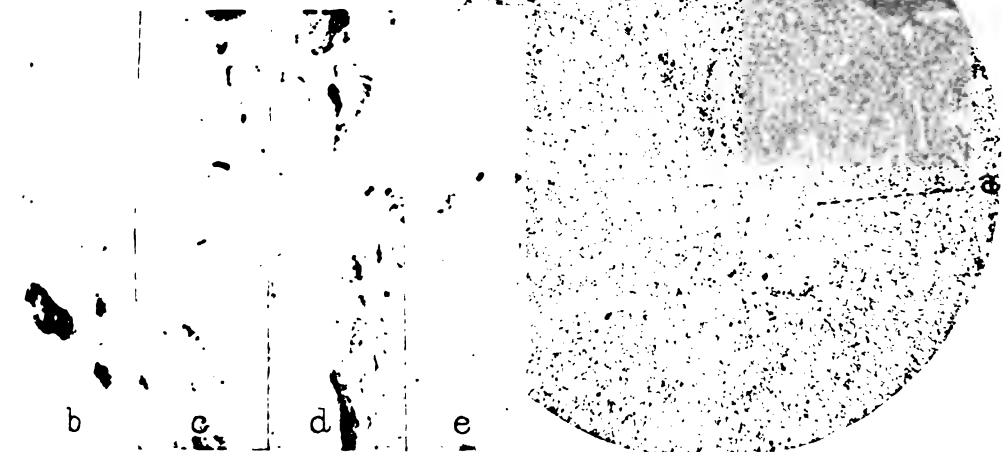


Fig. 255.

Fig. 257.

Fig. 254.—Microorganisms in nervous system of Case 714. ( $\times 1000$ .) *a*, Large and small elongated cocci in film from surface of cerebrum. Giemsa. *b*, Large and small diplococcus, medium-sized diplococci, and very small diplococci in contact film from surface of cerebrum. Gram-Weigert. *c*, Large and small diplococcus in edematous area in anterior horn of cervical cord. Gram-Weigert. *d*, Diplococcus in intervertebral ganglion. Gram-Weigert. *e*, Microorganisms in nervous system, Case 729. ( $\times 1000$ .) *a*, Diplococcus in contact film of cerebrum. Giemsa. *b*, Large coccus being into small diplococci and cocci, and a small, lightly stained diplococcus in contact film of cerebrum. Giemsa. *c*, Two medium-sized diplococci in chain and small diplococcus in pia near anterior fissure. Gram-Weigert. *d*, Three diplococci in pia near anterior fissure. Gram-Weigert. *e*, Diplococcus adjacent to leukocyte in edematous area in anterior horn of lumbar cord. Gram-Weigert.

Fig. 257.—Necrosis of lymph-follicle near base of tonsil, Case 712. Hematoxylin and eosin. ( $\times 40$ .)

colonies which grew only in the lower portions of the tube and which on being transferred to ascites-dextrose broth, showed large organisms varying greatly in size and shape, some resembling streptococci, other staphylococci and diphtheroid bacilli. These at first were considered contaminations, but since the different forms occurred in the same chain and developed in strains after repeated platings, fishing single colonies each time, under conditions in which entrance of extraneous organisms was carefully excluded, they were held to be variants or mutation forms. Moreover, by following the methods of cultivation described, the details of which are to be published in another paper, two strains of pure cultures of the "globoid" organism, obtained through the kindness of Dr. Noguchi, have been made to grow aerobically on repeated occasions. This has been done with cultures made from single colonies and in media where the possibility of contamination from the tissue and ascites fluid was excluded. In the aerobic condition the size, morphology, and character of growth resemble closely the aerobic form as we isolate it constantly from poliomyelitic tissue.

At first it was thought that the small globoid organism in ascites-tissue fluid (Fig. 262,b), as described by Flexner and Noguchi, was characteristic of this medium, but by making smears from the bottom of the tubes daily after inoculation, it was found that the minute forms observed after some days of incubation and after evidence of growth was apparent, were the result of the breaking down of larger forms present before clouding occurred. Mathers and Nuzum and Herzog have reported similar cultural results in cases of poliomyelitis, but appear to have overlooked this point. Kolmer, Brown, and Freese,<sup>7</sup> who also report similar findings, state that "Films of the aerobic and young anaerobic cultures showed a Gram-positive coccus, usually arranged in diplococcus formation in chains of four or five pairs and in clumps. Films of older anaerobic cultures (fourteen days or more) showed that the majority of these cocci had become smaller and many were easily decolorized by alcohol in the Gram stain."

A detailed study of this point was made by Rosenow and Towne with identical strains isolated from the brain and cord of monkeys paralyzed with virus in the usual way. By studying the method of growth in accordance with oxygen-tension the mechanism by which the large forms become small and the small forms large has been determined. They grow small in anaerobic cultures of ascites fluid plus tissue and oil and large in aerobic cultures of ascites-dextrose broth. Rosenow and

Towne have already suggested that "among many factors concerned in causing these changes in size, surface tension may be of importance. If there are so many large diplococci that their metabolic requirements cannot be met by the medium, division which gives more surface for the same sized body might allow a certain number of the resulting smaller forms to survive."

The growth of the small organisms to large size under aërobic cultivation in ascites-dextrose broth where oxygen and available nutrient material are abundant would seem to be the result of the same factors working in the opposite direction. It appears quite as if the alterations in size occur according as certain metabolic or oxygen requirements need to be maintained. The occurrence of large, medium-sized, and small forms in the tissues as shown in this paper would appear to be due to the same causes. The fact that large forms are prone to occur along blood-vessels in the tissues where available oxygen would appear to be relatively high is thus explained, and hence these large forms should not be considered as being contaminations or as distinct from the small forms. A certain degree of adaptation or alteration in these requirements, however, appears to take place, because the organism, when kept under strict anaërobic conditions for a long time, resists aërobic cultivation, a power which it can again be made to acquire gradually. The fact that unusually large forms are prone to develop when growth does occur (Figs. 262, *c* and 262, *d*) after anaërobic cultivation, and when first isolated from the tissues (Fig. 260), a property which is lost on continued aërobic cultivation, is also in harmony with this idea.

#### CHARACTERISTICS OF THE MICROÖRGANISM FROM POLIOMYELITIS

In Table 2 is given a summary of the morphologic character of growth on blood-agar, solubility in bile, etc., and the fermentative powers of strains isolated from tonsils and central nervous system of 35 cases of poliomyelitis. Altogether, the fermentative powers of strains from 49 cases have been studied, but the other tests were not made at the same time and hence are not included in the table. Twenty of the strains summarized in the table were isolated from the tonsils or the throat, 3 from stool, and 17 from brain or cord. The culture generation is indicated by the figure following the point and the animal passage by the exponent to the right and above the figure indicating the strain or case number. Standard blood-agar made from Liebig's extract of beef and Witte's peptone, to which about 0.3 c.c. per 5 c.c. of agar of

TABLE 2.—CHARACTERISTICS OF MICROORGANISMS

STRAIN	SOURCE	CHARACTER OF GROWTH ON BLOOD-AGAR PLATE	TURBIDITY	ASCITES-DEXTROSE BOTTLE	
				Sediment	Morphology
686.12*	Tonsil	Small dry colonies with green halo. No hemolysis	Diffuse granular cloud	Granular	Irregular short-chained streptococcus, some very small. Large and small forms in same chain
686.12	Tonsil	Small dry colonies with green halo. No hemolysis	Diffuse granular cloud	Granular	Irregular short-chained streptococcus, some very small. Large and small forms in same chain
686.2	Tonsil	Small colonies with green halo. No hemolysis	Diffuse granular cloud	Flocculent	Irregular short-chained streptococcus, some very small. Large and small forms in same chain
698.3	Tonsil	Grayish-green indifferent colonies	Diffuse granular cloud	..	Irregular diplococci in short chains
699.7	Tonsil	Small dry colonies with green halo	Diffuse cloud	Flocculent	Irregular diplococci in short chains
700.3	Tonsil	Small colonies with green halo	Diffuse cloud	..	Short-chained pneumococcus-like streptococcus
701.4	Tonsil	Grayish indifferent colonies	Diffuse cloud	..	Short-chained pneumococcus-like streptococcus
704.7	Tonsil	Moist colonies with green zone	Slight granular cloud	Flocculent	Irregular diplococci often a short chains
707.10	Cord	Small dry colonies with narrow green zone	Slight granular cloud	Flocculent	Irregular micrococci tetrad
707.4	Cord after in glycerin 16 months	Small dry colonies. Faint green zone in first two cultures then slightly hemolyzing zone	Diffuse granular cloud	Flocculent	Irregular short-chained streptococcus
708.10	Tonsil	Medium dry colonies	Diffuse cloud	Flocculent	Medium size, decidedly irregular diplococcus in short chains
708.15	Tonsil	Small dry colonies	Diffuse cloud	Flocculent	Medium size, regular short diplococcus in short chains
711.3	Tonsil	Small dry colonies with green halo	Diffuse cloud	Flocculent	Pneumococcus-like diplococcus in short chains
714.11	Brain	Small dry colonies with green halo	Diffuse cloud	Granular	Round short-chained streptococcus
714.18	Brain	Small dry colonies with green halo	Diffuse cloud	Granular	Irregular streptococcus. Revolution forms and coccoid dividing transversely
714.27	Tonsil	Moist colonies with green halo	Diffuse cloud	Flocculent	Small round regular micrococci
714.32	Brain	Moist colonies with green halo	..	..	..
714.47	Brain	Large moist colonies with green halo	Diffuse cloud	Flocculent	Round, medium short-chained streptococcus
714.3	Brain after in glycerin 16 months	Small dry colonies with green in first culture, slightly hemolyzing colonies in third culture	Diffuse granular cloud	Flocculent	Round short-chained streptococcus
721.5	Brain	Small dry colonies with green halo and larger more opaque grayish colonies	Diffuse cloud	Granular	Short-chain streptococcus of varying size and shape. Micrococcus forms and chains from single colonies
722.4	Brain	Small dry colonies with green halo	Diffuse cloud	Granular	Short-chain streptococcus of varying size and shape. Micrococcus forms and chains from single colonies
722.3.12	Brain	Translucent colonies	Diffuse cloud	Granular	Short-chain streptococcus of varying size and shape. Micrococcus forms and chains from single colonies
722.12	Brain	Small colonies with green halo	Diffuse cloud	Granular	Short-chain streptococcus of varying size and shape. Micrococcus forms and chains from single colonies
723.5	Tonsil	Chocolate-colored colonies	Granular cloud	Granular	Irregular diplococcus
474.7	Cord	Moderate moist colonies with green halo	Slight cloud	Granular	Irregular short-chained streptococcus hemolyzing pneumococcus

\* The small figure to the right of and above the decimal point indicates the animal passage; the large figure following indicates the culture generation.

## TED FROM ACUTE EPIDEMIC POLIOMYELITIS

MILK		GELATIN	PRECIPITATION IN ASCITES-DEX-TROSE AGAR	SOLUBILITY IN BILE	ACID PRODUCTION IN BROTH									
Decol-orization	Coag-ulation				Plain	Dex-trose	Lac-tose	Mal-tose	Saccha-rose	Raffi-nose	Man-nite	Salicin	Inulin	
0	0	0	+	0	0	+	+	+	+	No growth		..	0	
0	0	..	..	0	0	+	+	+	+	+ No growth		+	0	
0	+	..	..	..	0	+	+	+	+	+	No growth	0	0	
0	0	0	..	..	0	+	+	+	+	+	0	+	+	
0	0	0	+	0	0	+	+	+	0	0	0	+	0	
..	..	..	..	..	0	+	+	+	+	No growth 0		+	+	
..	..	..	..	..	0	+	+	+	+	+	0	+	+	
0	0	0	+	0	0	+	+	+	+	0	0	0	0	
0	0	0	+	..	0	+	+	+	+	+	0	+	0	
+	+	0	+	0	0	+	+	0	+	+	0	0	+	
..	0	+	0	0	0	+	+	+	+	+	0	0	0	
No growth		0	0	+	0	+	+	+	+	0	0	0	0	
+	0	+	0	0	0	+	+	+	+	0	0	0	+	
..	0	+	0	+	0	+	+	+	+	+	0	0	0	
+	+	+	0	0	0	+	+	+	+	+	0	0	0	
+	0	0	0	+	0	+	+	+	+	0	0	0	0	
..	..	..	..	..	0	+	+	+	+	0	0	0	0	
+	0	0	0	+	0	+	+	+	+	0	0	0	0	
+	+	+	Lique-hed	+	0	+	+	+	+	0	+	+	0	
+	+	0	0	+	0	+	+	+	+	+	+	+	0	
..	..	..	..	..	0	+	+	+	+	+	0	+	+	
..	..	..	..	..	0	+	+	+	+	No growth		+	+	
..	..	..	..	..	0	+	+	+	+	+	No growth		+	+
..	..	..	..	..	0	+	+	+	+	+	0	+	0	
0	0	0	0	0	+	0	+	+	+	+	+	+	+	

TABLE 2.—CHARACTERISTICS OF MICROORGANISMS

STRAIN	SOURCE	CHARACTER OF GROWTH ON BLOOD-AGAR PLATE	TURBIDITY	ASCITES-DEXTROROSE BOTTLE	
				Sedi- ment	Morphology
725.2	Tonsil	Chocolate-colored colonies	Slight cloud	Granular	Irregular short-chained micrococcus resembling micrococcus
729.10	Cord	Small moist and indifferent colonies	Diffuse cloud	Flocculent	Large oval diplococcus chains
729.7	Brain	Large moist indifferent colonies	Diffuse cloud	Flocculent	Medium round diplococcus
730.10	Tonsil	Small dry green colonies	Diffuse cloud	Flocculent	Small round diplococcus clumps and short chains
731.2	Tonsil	Grayish colonies	..	..	Small round diplococcus clumps and short chains
732.8	Tonsil	Small dry colonies with green halo	Granular cloud	Flocculent	Very irregular streptococcus short and long chains
733.2	Tonsil	Small dry colonies with green halo	Granular cloud	Flocculent	Very irregular streptococcus short and long chains
734.2	Tonsil	Small dry colonies with green halo	..	..	Very irregular streptococcus short and long chains
773.2	Stool	Moderate moist colonies with green halo	Diffuse	Slightly flocculent	Large micrococci singly or in diplococci and short chains
836	Brain or cord	Small dry colonies with green halo	Diffuse	Granular	Large oval diplococcus
837	Brain or cord	Grayish-green staphylococcus-like. Some hemolyzing colonies	Flocculent	Flocculent	Micrococcus type
838	Brain or cord	Grayish-green staphylococcus-like. Some hemolyzing colonies	Flocculent	Flocculent	Micrococcus type
839	Brain or cord	Indifferent staphylococcus-like colonies	Diffuse	Granular	Micrococcus type. Quadruple staphylococcus-like
840	Brain or cord	Small dry colonies; slight hemolysis around colonies	Diffuse	Granular	Large lanceolate diplococcus in clumps and short chains
841	Brain or cord	Small dry colonies; slight hemolysis around colonies	Diffuse	Granular	Large lanceolate diplococcus in clumps and short chains
842	Brain or cord	Small dry colonies with green halo	Diffuse	Granular	Large lanceolate diplococcus in clumps and short chains
890	Pons	Opaque grayish-green colonies	Slightly diffuse cloud	Flocculent	Micrococcus type. tetrad diplococci, and short chains
938.6	Tonsil	Small dry colonies with green halo	Diffuse cloud	Flocculent	Irregular short-chained streptococcus
938.7	Pons	Small dry colonies with green halo	Diffuse cloud	Granular	Irregular short-chained streptococcus
943.6	Stool	Small dry colonies with green halo	Granular cloud	Granular	Medium short-chained, elongated streptococcus
943.6	Tonsil	Small dry colonies with green halo	Granular cloud	Granular	Medium short-chained, elongated streptococcus
943.3	Brain	Small dry colonies with green halo	Granular cloud	Granular	Medium short-chained, elongated streptococcus
943.3	Lumbar cord	Small dry colonies with green halo	Granular cloud	Granular	Medium short-chained, elongated streptococcus
948.3	Tonsil	Large opaque colonies with greenish tinge	Diffuse cloud	Flocculent	Irregular diplococci, some very large, others medium size
948.3	Brain	Large opaque colonies with greenish tinge	Diffuse cloud	Flocculent	Irregular diplococci, some very large, others medium size
979.3	Stool	Small dry colonies with green halo	Diffuse cloud	Flocculent	Irregular diplococci, some very large, others medium size

defibrinated human blood was added, was used for the plates. Twenty-nine of these strains produced small, dry colonies with a green halo and sometimes slight hemolysis after from forty-eight to seventy-two hours: 7 produced somewhat more moist colonies with a greenish tinge resembling virulent pneumococci; 8 produced small grayish or chocolate-colored, indifferent colonies, and 7, larger, more opaque, grayish-white

## FROM ACUTE EPIDEMIC POLIOMYELITIS—(Continued)

S MILK		GELATIN	PRECIPITATION IN ASCITES-DEXTROSE AGAR	SOLUBILITY IN BILE	ACID PRODUCTION IN BROTH								
COLONIZATION	COAGULATION				Plain	Dextrose	Lactose	Maltose	Saccharose	Raffinose	Mannite	Salicin	Inulin
..	..	..	..	..	0	+	+	+	+	+	0	0	0
..	0	0	+	0	0	+	+	+	+	+	+	+	0
0	0	0	+	+	0	+	+	+	+	+	+	+	0
0	0	0	+	0	0	+	+	+	+	0	0	0	0
..	..	..	..	..	0	..	+	+	+	No growth	+	+	0
0	0	0	0	0	No growth	+	+	+	+	0	0	0	0
..	..	..	..	..	0	+	+	+	+	+	No growth	+	+
..	..	..	..	..	0	+	+	+	+	0	+	+	0
+	0	0	+	0	0	+	+	+	+	No growth	0	+	0
0	0	0	+	0	0	+	+	+	+	0	+	+	0
0	0	0	+	0	0	+	0	+	+	0	0	0	0
0	0	0	+	0	0	+	0	+	+	0	0	0	0
0	0	0	+	0	0	+	+	+	+	0	0	0	0
+	0	0	+	0	0	+	+	+	+	0	+	+	0
+	0	0	+	0	0	+	+	+	+	0	+	+	0
0	0	0	+	0	0	+	+	+	+	0	+	+	0
0	0	Liquefied	+	0	0	+	+	+	+	0	+	+	0
0	+	0	0	0	0	+	+	+	+	+	0	0	No growth
..	..	0	..	..	0	+	+	+	+	0	0	+	+
..	..	0	..	..	0	+	+	+	+	+	0	+	+
..	..	0	..	..	0	+	+	+	+	+	0	+	+
..	..	0	..	..	No growth	+	+	+	+	+	0	No growth	+
..	..	0	..	..	0	+	+	+	+	+	No growth	+	+
+	0	0	0	..	0	+	+	+	+	+	+	+	+
+	0	0	0	..	0	+	+	+	+	+	No growth	+	+
+	0	0	0	..	0	+	+	+	+	+	0	+	+

colonies resembling staphylococci. On this medium the organisms were quite uniform in size and resembled pneumococci but were usually smaller and free from demonstrable capsule. The growth in ascites-dextrose broth or dextrose broth in columns about 7 cm. tall of the strains soon after isolation were relatively slow. Diffuse turbidity or a flocculent growth collecting along the side of the tube was usually noted in



from forty-eight to seventy-two hours unless the inoculation was heavy, when marked growth occurred in twenty-four hours. After cultivation for a time the growth became more rapid. Most of the strains on isolation showed a preference for relative anaërobic conditions. It was the rule that growth in these tubes began at the bottom and was then forced slowly to the top as oxygen-tension was lowered and as the bacteria multiplied. Frequently the top 0.5 to 2 cm. were perfectly clear, especially in large amounts of medium in bottles, when the deeper layers showed dense growth. This clear layer was not observed in the tubes to which a thick layer of oil was added. The preference for relative anaërobic conditions was usually lost after a number of aërobic transplants, but it was preserved and at times was regained on anaërobic cultivation in ascites-tissue fluid.

The morphology in ascites-dextrose broth, as given in the table, varied considerably in the different strains and according to the time of and method of previous cultivation. In all but 7 strains the form was distinctly streptococcal, smears showing short chains of diplococci resembling pneumococci, a smaller number of medium-sized cocci in pairs of varying size, and occasional large and very small diplococcus and coccus forms (Figs. 260, 261, and 262). Most of the strains had been grown aërobically for some time and had lost much of the tendency to grow with marked variations in shape and size. They approached ordinary-sized diplococci or short-chained streptococci.

Practically all the strains acidified, but only a small number decolorized or coagulated litmus milk. Only one strain liquefied gelatin. Twenty of 27 strains produced clouding of ascites-dextrose agar; 3 of 26 were dissolved by bile. All produced acid in dextrose, maltose, and saccharose and all but 2 in lactose. Twenty of 45 strains produced acid in raffinose, 11 of 39 in mannite, 28 of 44 in salicin, and 17 of 48 in inulin. In 3 cases the strains from tonsil and brain or cord, in 1 case from tonsil, stool, brain, and cord, and in 5 cases the strain before and after from one to four animal passages showed practically identical fermentative powers. This was true in some instances in which a given strain was passed through different species of animals, and hence the strains isolated from the animals were not contaminants. The power to produce acid in inulin by these strains, as is true with pneumococci from lobar pneumonia, tends to be lost on prolonged cultivation, especially on blood-agar. Thus, 6 strains produced acid soon after isolation but not later in repeated tests. Of the total number of 141 cul-

tures in which the fermentation tests were made, 69 were made soon after isolation, 33 fermenting inulin, while of 72 in which the tests were made from three to fifteen months after isolation, only 7 fermented inulin. All the strains tested from the Davenport epidemic fermented inulin and all these tests were made soon after isolation. None of the Philadelphia strains\* (Cases 836 to 899) fermented inulin. All the tests were made after the strains had passed through numerous cultures.

It is noteworthy that none of the 3 strains isolated from the stool in 3 cases fermented mannite, and hence they should not be regarded as *Streptococcus faecalis*. The morphology and character of growth resembled closely the strains isolated from the tonsil and nervous system. Moreover they had common agglutinative properties.† Gastro-intestinal symptoms were pronounced in each of these patients. The remaining 7 strains showed large diplococci singly, in masses, and rarely in short chains. Mathers, and Nuzum and Herzog, and Kolmer, Brown and Freese also report the isolation of these 2 types of strains. The former consider them as the same organism, the latter as distinct. These strains produced larger and more opaque colonies than the streptococci. It has frequently happened that both these types have been isolated from the same case, both varieties have developed from widely separated single colonies and from pure cultures of the streptococcus after repeated platings. The diplococcus or micrococcus type of growth is particularly prone to develop from the streptococcus when pure cultures of the latter in old anaërobic cultures in ascites fluid plus tissue and oil or ascites-tissue-agar stabs are transferred to dextrose broth and then plated, or to blood-agar plates directly. Observations made in Case 721 are similar to many others that have been made:

*Sept. 5, 1916.*—Smears from single colonies in ascites-dextrose-agar and dextrose-agar shake-cultures showed chains and pairs, some evidently streptococcus, others resembling staphylococci. Blood-agar plates showed pure culture of small, dry, green colonies. One of these colonies was stabbed and inoculated into the agar.

*Sept. 9.*—Blood-agar plate from stab made from above colony in dextrose-agar again showed pure culture of small, dry, green colonies. Single colonies from blood-agar plate to blood-agar plate were now transferred daily for six days. The power to produce green colonies gradually diminished, but otherwise pure, fine, dry colonies were obtained in each

\* We are indebted to Dr. B. Lucke and Dr. M. Solis-Cohen for these strains.

† For the agglutinating power of these strains and their infective power reference is made to other papers in this series.

plating. A single colony was again plated and inoculated into a tall tube of dextrose broth. The plate-to-plate culture again showed fine, dry colonies. Platings from the broth the following day yielded countless small colonies a little more moist than before and showing no green or hemolysis; among them were larger, more opaque, staphylococcus-like colonies with large diplococci and tetrads. The latter resembled exactly those obtained with the streptococcus from dextrose-broth cultures of the emulsion of the brain and cord in this case, and until this observation was made were considered contaminations. A close distinction, therefore, between these two forms should not be made.

CASE 695.—N. L., a boy, aged four years. (Patient of Dr. G. T. Joyce, Rochester, Minn.)

*July 28, 1916.*—The illness began with cough, headache, high fever, and marked constipation. Flaccid paralysis of the right leg developed on the second day, of the right arm and left leg on the third, and marked weakness of the left arm and difficulty in breathing on the fourth. Much mucopurulent material was found in the nasopharynx. The throat was moderately red. The tonsils were small and appeared quite normal on the surface but pus was expressed. The spinal fluid was under pressure and clear. The patient recovered with marked persistent residual paralysis. This child, together with his older brother, aged six years, had an attack of bronchitis with fever about ten days previous to the onset of the paralytic attack. Both showed a recurrence of the bronchial infection, but the older brother recovered without developing paralysis.

*Aug. 3.*—Blood-agar plate of pus from tonsil showed enormous numbers of fine, dry colonies with a green halo, a few fine hemolyzing colonies, and a few larger, more opaque colonies.

*Aug. 4.*—Blood-agar plate of pus obtained from tonsil the second time showed a similar result. Ascites-dextrose-broth cultures from pus and from single colonies showed streptococci varying greatly in size and shape. In some instances very large budding forms were seen in chains containing typical diplococci. Large coccus-like forms in chains were seen to break into two and four smaller forms (Fig. 260). Cultures from the tonsil on three subsequent dates showed a gradual diminution in the number of fine, dry, hemolyzing colonies.

CASE 707.—W. M., a boy, aged four years, was admitted to the New York Hospital Aug. 18, 1916. The disease began six days previously with high fever and vomiting, after which the child was better for three days. He grew nervous and restless and again vomited a number of times three days previous to admission to hospital, developing weakness and asymmetry of the left side of the face and difficulty in swallowing. The patient was inert and stuporous, with rigidity of neck and back. The respirations were rapid and performed mostly with the accessory muscles. He cried out weakly and was unable to take food. A spinal

puncture was made; the fluid was not under increased pressure and 15 c.c. were withdrawn. There were 40 cells per cubic millimeter.

*Aug. 19.*—The child died of respiratory failure. There was a rise of temperature to 103° F. immediately before death. This patient had had tonsils and adenoids removed several months previous to the attack of poliomyelitis. A partial necropsy was obtainable. There were edema and hemorrhages of the dura, marked congestion of the vessels of the pia of the cord associated with marked edema, a thin fibrinous film covering the pia, and a markedly increased amount of clear spinal fluid. Cross-sections of the cord showed extreme hyperemia of the vessels, hemorrhages, and edema, especially of the gray matter of the anterior horns. The spinal ganglions appeared edematous. One and one-half centimeters of dorsal cord were removed in a sterile manner, emulsified in a sterile air chamber, and cultures made immediately in dextrose-agar and ascites-dextrose agar, in ascites tissue fluid covered with paraffin-oil, and in plain and dextrose broth with and without sterile ascites fluid.

*Aug. 21.*—Ascites-dextrose broth showed granular turbidity, and smears showed large numbers of large and small Gram-positive and Gram-negative diplococci and short chains. The larger organisms resembled pneumococci. Films from one colony 1.5 cm. from the top of the ascites-dextrose-agar shake culture showed large, lanceolate-shaped and smaller, more rounded diplococci. Sometimes both varieties occurred in the same chain. No other colonies were detected in the shake cultures. Ascites-fluid culture showed no increase in turbidity. Ascites-dextrose-broth culture showed diffuse granular cloud and stained films, short-chained, irregular streptococcus.

*Aug. 23.*—Blood-agar plate cultures of each of these showed pure growth of fine, dry, non-adherent colonies of streptococci surrounded by a faint green zone. The blood-agar plates which had been inoculated with the single colony in dextrose-agar were used to inoculate ascites-dextrose broth, and tall tubes of ascites-plain-tissue broth and ascites-tissue fluid to which a layer of oil was added.

*Aug. 24.*—The dextrose-broth culture showed diffuse granular cloud with flocculent sediment and many Gram-staining diplococci of irregular size. The ascites-plain-tissue broth and ascites-tissue fluid showed no turbidity.

*Aug. 26.*—The latter two cultures showed a dense collection of fine colonies in the bottom, appearing as a granular growth loosely adherent to the side of the tubes. These became gradually fewer in number and smaller in size up to 3.5 cm. from the top. Above this point the mediums were clear. Smears showed lanceolate diplococci, a great many round, coccus-like bodies, occasionally in short chains, some as large as *Staphylococcus albus*, others much smaller.

*Aug. 28.*—Smears from the bottom of the ascites-tissue-fluid culture showed an occasional large diplococcus and chains of diplococci and a

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terial, softer and more opaque than the collections of cells from swollen follicles. Smears showed large and small mononuclear cells, leukocytes, débris, and later enormous numbers of diplococci of medium size, large and small coccus and diplococcus forms, and occasionally fusiform bacilli. The small forms resembled "globoids," but no sharp line could be drawn between these and the larger forms; all types were often seen in the same chain. On the basis of these striking findings, and after it had become evident that the organisms were of low virulence, it was determined, through the coöperation of Dr. J. C. Roper, to remove the tonsils in a series of patients who were not convalescing satisfactorily and in whom a low grade of fever persisted. This was done in 11 cases. In 3 patients there was a slight temporary rise in temperature, in 5 the temperature curve was not altered, and in 3 it was definitely lowered. Seven of the patients showed improvement in their general condition—they were brighter and less irritable. In the others no noticeable change occurred.

During tonsillectomy a large amount of infected material was noted, and in all one or more small abscesses were found in the tonsils on making sections. These abscesses were less prominent than in the fatal cases. Similar abscesses and identical organisms were found in adenoids removed before and after death. Sections of the tonsils showed marked hyperplasia of the lymph-follicles, and in all but 2 of the 14 cases studied one or more small or large areas of necrosis in lymph-follicles (Table 1 and Fig. 257). The exudate in the crypts contained leukocytes, round-cells and many cocci and diplococci and moderate numbers of fusiform and other bacilli. In a number of instances the epithelial lining of the crypts showed atrophy but usually this could not be made out.

The cells in the necrotic areas in the follicles were chiefly large and small mononuclears, although in some instances a large number of leukocytes were present. Many large and small cocci and diplococci, exactly like those found in small numbers in the brain and cord and mesenteric glands, were found in these areas. Bacilli were almost wholly absent. Excellent opportunity to study the relationship between large and small forms was here afforded, and in a number of instances unmistakable evidence of large coccus and diplococcus forms breaking into the smaller cocci were discovered (Figs. 258 and 259). The number of bacteria demonstrable within swollen follicles was surprisingly small. Those found corresponded very closely in size and shape to the cocci found in the cord and mesenteric lymph-glands. Bacilli were never found in

swollen but otherwise normal follicles. In a number of instances a large number of cocci and diplococci were found in areas of round-cell infiltration, in the capsule of the tonsil, and around large blood-vessels outside the capsule. A few were found in blood-vessel walls and within the lumen of blood-vessels.

In the Davenport epidemic a study of the relation of infection in tonsils to enlargement of cervical lymph-glands immediately outside the tonsils was made in 38 cases. In 26 of these the cervical glands were enlarged, and in 11 the enlargement on either side was in proportion to the amount of infection in the tonsil on the corresponding side, as determined by the greater size of the tonsil or larger amount of infected material which could be expressed. In several instances these findings were verified at necropsy. No definite relation between infected conditions of the teeth could be made out although caries was present in some of the cases. The tonsils from 12 persons removed for various reasons in other diseases have been examined in the same way. The abscesses in the lymph-follicles on cross-section and the areas of necrosis noted microscopically in poliomyelitis were not found, although abscesses in crypts containing many organisms with atrophy of the epithelium were found in some of these.

The results of the study of the tonsils and adenoids here reported indicate strongly that these structures afford important entrance ways for the microörganisms which we find constantly in the diseased tissues in poliomyelitis. A relatively large amount of infected material may be expressed from the tonsils. The abscesses and areas of necrosis are more numerous and are larger in the fatal cases than in tonsils removed from convalescent patients. These abscesses contain large numbers of this microörganism, particularly in the fatal cases, and the cocci have been demonstrated in tissues immediately outside the tonsils, in areas of infiltration along large blood-vessels and within the lumen of capillaries. Injection of cultures into animals produced flaccid paralysis. Removal of tonsils and adenoids in convalescent patients has been followed by seemingly good effects in some instances. In view of these facts there can be little doubt but that diseased tonsils and adenoids predispose to poliomyelitis and may lead in some instances to severe or fatal infection which might otherwise be mild. The focal areas of infection with abscess formation in these structures may be an important factor in prolonging an attack, in preventing early restoration of lost muscle function, and be the cause of remissions or relapses which

occur not infrequently, as pointed out especially by Wickman and by Draper. The abscesses are usually small, and so situated mechanically as not to interfere with their healing. Protection by removal of these structures is only relative at best and temporary entrance channels for bacteria are made by their removal. Hence their wholesale extirpation for protection against this dread disease would not be justified. Their removal in special instances may be useful, but the well-established principles for the removal of tonsils and adenoids as applied in connection with other conditions should be followed in this disease.

#### SUMMARY

A pleomorphic coccus has been isolated from and demonstrated in affected tissues in all the cases examined of poliomyelitis that occurred in different epidemics and in widely separated parts of the country. The organism has been found in large numbers in adenoids and tonsils, in smaller numbers in lesions in various parts of the central nervous system, and in the mesenteric lymph-glands. It has been proved to be absent in organs showing no lesions. The organism shows great variations in size and shape, depending on the method of cultivation. In aerobic cultures, although more irregular in size, it closely resembles ordinary green-producing streptococci or pneumococci of low virulence. Under anaerobic cultivation, especially in tall columns of ascites fluid plus tissue and oil, it grows to very small size, becomes filtrable, and in every way appears identical with the "globoid" organism described by Flexner and Noguchi. The variations noted in cultures have been proved not to be due to contaminations or to mixed cultures. All graduations in size between large coccus or diplococcus forms to exceedingly small, almost ultramicroscopic forms, were found alike in cultures and in the tissues, and the conditions favorable for the formation of one from the other have been determined. Morphologic evidence of the breaking down of large forms into the small forms in the tissues has been obtained. Pure cultures of this organism have been isolated many times and it has been demonstrated in films and sections of brain and cord many months after they were placed in 50 per cent glycerol. In view of these results the presence of this organism in the diseased tissues cannot be considered an accidental contamination.

The following facts, determined since the studies reported in this paper were begun, indicate that the organism here described bears etiologic relationship to poliomyelitis. It is constantly present in the

diseased tissues, from which it can be cultivated even many months after glycerolation. On injections of cultures into young rabbits and guinea-pigs it localizes specifically in the nervous system and produces flaccid paralysis and changes in brain and cord which resemble those in poliomyelitis in man.<sup>20</sup> From the brain and cord of these animals the organism can be isolated and the disease again produced. The organism has been rendered filtrable. By means of the same methods the identical organism has been isolated constantly from the brain and cord of monkeys paralyzed with fresh, glycerolated and filtered virus.<sup>19</sup> The serums of persons and of monkeys having recovered from poliomyelitis agglutinate specifically the more sensitive strains both from human and monkey poliomyelitis.<sup>18</sup> Injections of the recently isolated aërobic cultures into monkeys render them refractory to virus. The aërobic form of the organism from human and monkey poliomyelitis produces antibodies in the serum of horses, in a large amount common for both, cross-agglutinating these strains specifically in high dilution.<sup>19</sup> The serum of a horse immunized with freshly isolated strains from monkeys protected monkeys relatively against intracerebral inoculation of virus<sup>16</sup> and had pronounced curative effects in the treatment of human poliomyelitis. Early intravenous injections were followed by almost immediate cessation of symptoms in a large series of cases.<sup>17</sup>

The results of Flexner and Noguchi, so far as the cultivation of a small filtrable organism and its demonstration in the tissues in poliomyelitis are concerned, have been corroborated, but the results of our experiments indicate that this is the anaërobic and, according to Amoss' results, a non-antigenic form of the organism which, under aërobic cultivation, clearly belongs to the streptococcus group of microörganisms. Both forms have been constantly demonstrated side by side in the tissues of poliomyelitis. Flaccid paralysis coming on soon after injection has been produced in monkeys with characteristic, although not typical changes in the cord with aërobic cultures, but the classic picture as obtained with virus in this species has not been secured. It may be suggested, however, on the basis of results already obtained, that this is due to the development of antibodies, since the organism in the aërobic form has marked antigenic powers.

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# REPORT ON THE TREATMENT OF FIFTY-EIGHT CASES OF EPIDEMIC POLIOMYELITIS WITH IMMUNE HORSE SERUM\*

E. C. ROSENOW

It is my purpose in this paper to report in detail the results obtained from the serum treatment of 58 cases of poliomyelitis which occurred in Davenport, Iowa, and the surrounding locality during the latter part of the summer and in the autumn of 1917.

The details of the immunization of the horse whose serum was used, the effect of this immune serum on the virus of poliomyelitis in vitro, its protection and curative power against experimental poliomyelitis in the monkey, its agglutinin and other antibody content,<sup>8</sup> and its effect in 44 cases of human poliomyelitis, have already been published.<sup>9</sup> Suffice it to point out here that the horse was injected at intervals (from Nov. 2, 1916, to May 1, 1917) with increasing doses of pure cultures of the pleomorphic streptococcus isolated a short time previously from the central nervous system of monkeys paralyzed with virus. Altogether the growth from 42,200 c.c. of broth was injected.

## DIAGNOSIS

The diagnosis was made in the cases treated on the combined clinical and spinal-fluid findings. All patients presenting symptoms of an acute infection with unusual evidence of involvement of the central nervous system were subjected to spinal puncture. If the spinal fluid was under increased pressure, if it was clear or only slightly turbid, and if it contained an abnormal number of cells—chiefly mononuclear—and an increased globulin content, as determined immediately at the bedside by a count and Noguchi's globulin test, the diagnosis of poliomyelitis was made and the serum was given at once.

In all cases there was more or less fever, often high at the onset, which usually began without a chill. Gastro-intestinal symptoms were

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pronounced in the epidemic and were frequently initial, especially in children. Vomiting and diarrhea occurred in most instances and persisted in some. At first the vomitus contained undigested food, though later, in the severe cases, it contained large amounts of mucus and coffee-ground material. There was a great deal of mucus in the stools, and at times blood and bloody pus. The pulse-rate was unusually rapid and out of all proportion to the evidence of general intoxication. Headache, irritability, and restlessness, followed by abnormal apathy or drowsiness, tremor, twitching of various muscles, pain in one or more extremities or in the back or neck, ataxia, retraction of the head, rigidity and tenderness of neck and spine, disturbed reflexes, and Kernig or Babinski signs, were the chief symptoms which usually preceded the onset of paralysis and led to the tentative diagnosis of poliomyelitis and immediate spinal puncture for further diagnostic tests.

#### TECHNIC OF TREATMENT

In making the spinal puncture a needle of the usual type, but 2 cm. shorter, with a sharp, polished edge was used. In babies the puncture was made through the interspace, one, two or three spaces higher, depending on the age of the patient, than the one on the level of the crest of the ilium. A point just below and a little toward the side on which the patient was lying was selected for the puncture. The skin was sterilized with iodine or alcohol. The needle was inserted slowly through the skin and then carefully through the deeper layers, directing it slightly upward and aiming for the median line. The puncture was made just through the dura, which can easily be felt. In this way trauma and pain were reduced to a minimum and the fluid was obtained without the admixture of blood. The fluid was made to flow slowly and only moderate amounts were withdrawn. The intravenous injections were made through a fine needle (20 to 23 caliber) with 10 or 20 c.c. syringes of the Lürer type. Superficial veins at the bend of the elbow, about the wrists, ankles, or dorsum of the hands were used chiefly. In babies the injections may be made in the jugular vein.

The serum used was obtained from the horse on May 16. It agglutinated homologous and heterologous strains of the pleomorphic streptococcus in dilution up to 1:100,000 and protected monkeys against virus. It was preserved in the ice-chest after adding 0.2 per cent purified cresol. Aërobic and anaërobic cultures proved sterile on repeated occasions. Previous to administration it was usually activated with

guinea-pig complement by adding 1 part of fresh guinea-pig serum to 9 parts of the serum, thoroughly mixing and incubating at 37 C. for one hour.\* To facilitate slow injection and a more rapid diffusion in the blood, the activated serum was diluted with equal parts of 0.83 per cent salt solution. The injections were made slowly intravenously, not later than thirty-six hours after activation. About 1 c.c. of serum or 2 c.c. of the diluted serum were injected per minute. The dose was varied according to the age of the patient and the severity of the symptoms. The dose as reported in my preliminary report was practically doubled later and with seemingly greater benefit. Inquiry as to whether or not the patient had had diphtheria or tetanus antitoxin or horse serum was made in each case. If any of these serums had been given the patient was first desensitized, provided his condition allowed it, by injecting a small amount (0.5 c.c.) subcutaneously or 0.25 c.c. intravenously, one-half to two hours previously. Babies up to two years of age were given from 5 to 15 c.c. of serum, that is, 12 to 30 c.c. of the diluted serum; children from two to five years, 10 to 20 c.c.; from five to twelve years, 15 to 30 c.c.; from twelve years up, 20 to 50 c.c. All patients with a positive diagnosis and in whom the disease was still active were given the serum treatment irrespective of the severity or type of the disease. The injections at first were usually given once in twenty-four hours. Later they were repeated in from four, eight, twelve, to twenty-four hours as necessary. The return of fever and high pulse-rate after the initial drop which occurred commonly and the return of symptoms referable to the central nervous axis (irritability, twitchings, pain in extremities, rigidity of neck, etc.) after a primary disappearance or diminution, or the persistence of these symptoms, were considered indications for the giving of more serum.†

#### GROUP 1. CASES SHOWING NO PARALYSIS AT THE TIME OF SERUM TREATMENT

CASE 936.—K. K., a boy, aged nine years. (Patient of Dr. W. Matthey, Davenport, Iowa.)

\* Dr. George Braunlich, who carried on the treatment after October 1, reports getting apparently as beneficial results with the serum directly injected unactivated as with the activated serum. Hence injection of the serum without activation, preferably diluted with equal parts of salt solution, is recommended in instances in which activation would consume valuable time or be impracticable.

† I wish to express my appreciation to the physicians for their coöperation, to Dr. W. H. Rendleman, in particular, for notifying me of the epidemic, to Dr. George Braunlich for continuing the treatment, and for the use of the pathologic laboratory at Mercy Hospital.

*Sept. 1, 4 P. M.*—The boy had had diarrhea two days before. Headache, restlessness, and fever began the previous day, and he was unable to sleep during the night. He had an attack of vomiting in the morning which persisted most of the day. There were tingling and a numb feeling in the hands. He was irritable and nervous, the head was retracted and the knee-jerks were exaggerated. The throat was red and hyperemic; the tonsils were large, especially the right; the cervical gland outside the right tonsil was also enlarged. There was no evidence of weakness. The temperature was 101, the pulse 120. A spinal puncture was made; the fluid was under moderate pressure and 15 c.c. were obtained. Cell count 60, globulin test ++. Ten c.c. of serum were given.

*Sept. 2, 9 A. M.*—The headache continued into the night; the temperature by midnight was 103 F. The headache and temperature then rapidly disappeared. There was no weakness and the child felt well.

This patient made a complete recovery without evidence of paralysis.

CASE 944.—M. R., a boy, aged eleven years. (Patient of Dr. R. R. Kulp, Davenport, Iowa.)

*Sept. 7.*—There had been general irritability and restlessness with persistent headache and high fever ranging from 102.5 to 104 for four days previously. The child vomited four days before and complained of a sore throat, stiffness in the neck and severe pain in the back, especially when trying to get up. He was delirious part of the time at night. The throat and tonsils were unusually red, but there was no cryptic material and no pus was expressed. *7 P. M.*—There was a moderate stiffness of the neck and back. Attempts at flexion caused pain. The left knee-jerk was diminished and the right exaggerated. There were no twitchings, but a moderate mental apathy. The temperature was 104.4. A spinal puncture was made; the fluid was under pressure and 15 c.c. were obtained. Cell count 16, globulin test +. Twelve c.c. of serum were given.

*Sept. 8.*—The white blood count was 18,000; Widal test negative; temperature 103 F. No paralysis could be made out. The general condition was about the same.

*Sept. 9.*—The temperature was 100; the child felt better and looked brighter but still complained of some stiffness of the neck. The pain in the back had disappeared. The right knee-jerk was normal, the left was still somewhat sluggish.

*Sept. 10.*—He felt perfectly well and there was no paralysis.

*Sept. 23.*—A typical attack of serum disease occurred following overexertion the previous day.

*Oct. 15.*—The child was perfectly well. There was no paralysis at any time.

CASE 950.—M. C., a girl, aged two years. (Patient of Dr. F. Neufeld, Davenport, Iowa.)

*Sept. 12.*—She felt well until two days previously in the afternoon, when she became unusually restless and later drowsy. She was very drowsy and sleepy the next day; slept most of the time with the head retracted. The mother became alarmed because of peculiar jerking of the muscles of the arms, especially when the child was asleep. 8.30 A. M.—The temperature was 101.5. There were twitchings of the muscles of the hands, she was tremulous on getting up, and ataxic in walking. She slept most of the time. 12 M.—The temperature was 101.5. The head was retracted, the neck stiff, and the knee-jerks exaggerated. She was tremulous and there were twitchings of the muscles of the arms. No weakness was demonstrable. A spinal puncture was made and the fluid found under pressure. Cell count 150, globulin test +. Six c.c. of serum were given.

*Sept. 13, 8 A. M.*—She slept most of the night, with slight twitchings. The temperature was 98.8, the pulse 110.

*Sept. 14.*—She appeared well; the temperature was 98. She slept well all night and was bright and happy the next morning. No weakness was evident.

*Oct. 15.*—Attack of urticaria one week following injection of serum. Perfectly well.

CASE 953.—N. W., a boy, aged three years; brother of Case 948. (Patient of Dr. F. Neufeld, Davenport, Iowa.)

*Sept. 13.*—The child was well until the previous night, when he seemed feverish; the temperature was 100.5. He vomited at 11 o'clock and then slept the balance of the night. He was drowsy all the next forenoon. 12 M.—There was a slight rigidity of the neck. The tonsils were hyperemic and large; no attempt was made to express pus. There was an enlarged lymph-gland on either side just outside the tonsil. The right knee-jerk was exaggerated, the left diminished. Kernig was evident on both sides. There was twitching of the muscles of the right hand and fingers. The child appeared abnormally drowsy. The temperature was 101.5, the pulse rapid. There was no weakness. 12.30 P. M.—A spinal puncture was made, with spurting of fluid, and 10 c.c. were obtained. Cell count 18, globulin test +. Ten c.c. of serum were given. 1.30 P. M.—The child appeared brighter, was interested in surroundings, smiled, and appeared quite normal. The rigidity of the neck was less marked. 7 P. M.—The patient was bright, talkative, and alert. Supper was eaten with relish. The temperature was 101.

*Sept. 14.*—He appeared well. The temperature was 99. The knee-jerks were normal. Rigidity of the neck and Kernig were absent. There was no weakness.

*Oct. 15.*—The child was perfectly well.

(Temperature and pulse curves, Chart 1.)

CASE 954.—A. J., a boy, aged nine years. (Patient of Dr. F. Neufeld, Davenport, Iowa.)

*Sept. 13.*—He had had headache in the afternoon four days before, followed by pain in the back of the neck and high fever. The next day he had pain in the abdomen, followed by severe diarrhea a day later. He had no appetite. 4 P. M.—The temperature was 103, the pulse 134. The tonsils were large and pus was expressed from the left with slight pressure. They were diffusely red and there was one large lymph-gland adjacent to each tonsil. The teeth were normal. The abdomen was diffusely tender on deep pressure. There was no tenderness at McBurney's point. The knee-jerks were normal on the right side, but sluggish on the left; response was obtainable only on reinforcement. There was twitching of the hands and a slight ataxia in walking. The back and neck were held rather rigid and the Kernig sign was present. A spinal puncture was made; the fluid was under moderate pressure and

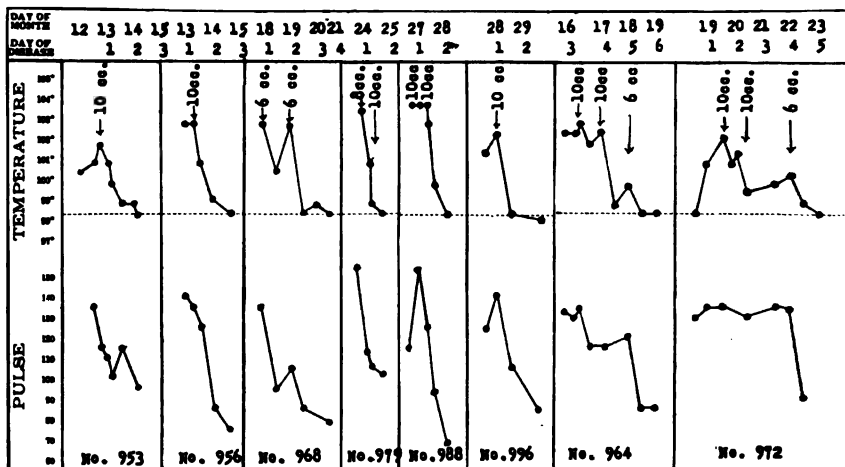


Chart 1.—Temperature and pulse curves of patients showing no paralysis at the time of serum treatment.

3 c.c. were obtained. Cell count 11, globulin test +. Twelve c.c. of serum were given.

*Sept. 14, 8 A. M.*—The temperature was 99.4. 6.30 P. M.—The temperature was 100.2 F., the pulse 112. The right knee-jerk was normal, the left still weak. The child appeared well. The headache had disappeared; the stiffness of the neck and Kernig sign were absent, and he walked without difficulty. There was no ataxia or weakness. 9.10 P. M.—Five c.c. of serum were given.

*Sept. 18.*—The temperature was normal. There was no weakness and the boy appeared well.

*Sept. 24.*—The child had felt perfectly well until the morning, when a typical mild attack of appendicitis developed, from which he recovered without surgical interference.

*Oct. 15.*—Recovery was complete.

CASE 956.—G. M., a boy, aged five years. (Patient of Dr. F. Neufeld, Davenport, Iowa.)

*Sept. 13.*—The patient was well until 4 o'clock in the afternoon, when he went into the house complaining of a severe headache. He became very ill shortly afterward, and at 8.30 that evening was tremulous, vomited, and had severe diarrhea. The temperature was 103 F., the pulse 145. *12 P. M.*—He was lying in bed with head retracted and was very dull mentally. He could be aroused but would promptly fall back to sleep. Attempts at flexion of the head caused pain. The Kernig sign was elicited on both sides. The eyes were dull. He was tremulous and there were twitchings of various muscles. The tonsils were normal in size and the pharynx was normal. The knee-jerk on the right side was exaggerated. There was no weakness. The child appeared extremely ill. He vomited a large amount of mucus streaked with blood. There was a marked diarrhea, the stools containing a large amount of mucus, some of it streaked with blood. The temperature was 103, the pulse 140. A spinal puncture was made; the fluid was under moderate pressure and 10 c.c. were obtained. Cell count 44, globulin test +. Ten c.c. of serum were given.

*Sept. 14, 8.30 A. M.*—The temperature was 101, the pulse 130. The child looked brighter. Some stiffness of the neck was still evident and there was slight Kernig. The left knee-jerk was normal, the right somewhat diminished. He complained of pain in the abdomen. *6 P. M.*—The temperature was 99.2, the pulse 90. He looked well and was hungry; the bowels were still loose. The neck was slightly rigid, the knee-jerks were normal, and he walked without ataxia. No evident weakness. Five c.c. of serum were given.

*Sept. 15.*—The child appeared perfectly well. The temperature was 98.6 F., the pulse 80. There was no weakness.

*Oct. 15.*—Recovery was complete.

(Temperature and pulse curves, Chart 1.)

CASE 962.—E. H., a young woman, aged twenty-four years. (Patient of Dr. L. F. Newburn, McCausland, Iowa.)

*Sept. 15.*—There had been malaise and she was generally below par for three or four days. She became extremely tired the day before, presumably from overexertion. She had been unable to sleep the night before on account of restlessness and pain in the abdomen. A number of loose bowel movements had occurred that day. She had severe headache in the afternoon. The temperature was 102 F., the pulse rapid. She was menstruating. *11.30 P. M.*—The patient had severe headache and pain in the back and felt very weak. There were twitchings of the muscles of the legs and a moderate rigidity of the neck. Flexion of the head caused pain. The knee-jerks on both sides were very weak, barely obtainable even on reinforcement. The tonsils were large and there was a diffuse hyperemia of the throat and mucus in the

nasopharynx. One large cavity was found in a left lower molar. The face was flushed. The temperature was 103.5, the pulse rapid. A spinal puncture was made; the fluid was under pressure and 20 c.c. were obtained. Cell count 23, globulin ++. Twelve and one-half c.c. of serum were given.

*Sept. 16.*—The physician found the patient sitting at the breakfast table. The headache had disappeared within one hour after the injection of the serum. The temperature was normal. There was no weakness.

*Oct. 14.*—The patient was perfectly well.

CASE 964.—H. J., a girl, aged four years, sister of Case 972. (Patient of Dr. A. Grassau, Princeton, Iowa.)

*Sept. 16.*—The child was perfectly well until two days before, when she had fever and was cross and irritable. The nose was discharging. She seemed abnormally drowsy. The condition was much the same the day before, but peculiar jerking of the muscles had developed in the extremities. She complained of headache in the morning and had six attacks of convulsive jerking of the extremities. She appeared confused mentally. *11.30 P. M.*—The face was symmetric, flushed, and she lay with head retracted. She was tremulous, ataxic, scarcely able to walk. Attempts to flex the head caused pain. She was very drowsy but could be aroused. The knee-jerks were exaggerated—more on the right side than on the left. Kernig and Babinski signs existed on both sides and hyperesthesia was noted. The tonsils were large and red. Much mucus was found in the nasopharynx. There were two palpable lymph-glands outside either tonsil. The thyroid was enlarged. There was marked ataxia, and peculiar spasms of the muscles of the arms and face. The child appeared very ill, was very tremulous and ataxic, and could scarcely walk, but there was no weakness. Spinal puncture was made; the fluid was under pressure and slightly turbid and 10 c.c. were obtained. Cell count 211, globulin test +. Ten c.c. of serum were given.

*Sept. 17, 6 P. M.*—She lay quiet in bed, the face was flushed, and the head retracted. The stiffness of the neck was less marked. Kernig was absent. The tremor and twitching of the muscles had disappeared. The face was symmetric. She was mentally brighter and there was no weakness. Ten c.c. of serum were given.

*Sept. 18, 6 P. M.*—She looked bright and appeared well. There was no retraction of the head. The pain and stiffness of the neck had disappeared. The knee-jerks were normal and there was no rigidity of the neck and no weakness. Six c.c. of serum were given.

*Sept. 19.*—She appeared perfectly well and without demonstrable weakness.

*Oct. 14.*—The child was perfectly well.

(Temperature and pulse curves, Chart 1.)

CASE 966.—H. S., a boy, aged three and one-half years. (Patient of Dr. E. O. Ficke, Davenport, Iowa.)

*Sept. 17.*—He had vomited three or four times two nights before and was restless all night. He was feverish and unusually drowsy the next day and complained of headache and pain in the back. There was looseness of the bowels. Marked tremor of various parts of the body was noted in the forenoon. The gait was ataxic. The knee-jerks on the left side were exaggerated and on the right side diminished. 5 P. M.—There was a moderately severe cough. The tonsils were large. There was one lymph-gland palpable on either side of the neck adjacent to the tonsil and the thyroid was distinctly enlarged. The head was retracted and the neck was definitely stiff. Attempts to flex the head caused pain. There was a marked tremor of the muscles of the hands and legs, and the gait was ataxic. The knee-jerk on the left side was exaggerated and on the right side diminished. The temperature was 103 F., the pulse 152. A spinal puncture was made, with spurting of fluid, and 12 c.c. were obtained. Cell count 27, globulin test ++. Ten c.c. of serum were given.

*Sept. 18.*—One hour after the injection of serum the previous day the boy appeared more tremulous and the head more retracted. 8 P. M.—The temperature was 103.6 F., the pulse 148. Seven and one-half c.c. of serum were given.

*Sept. 19, 10 A. M.*—There was herpes of the lips and nostrils. The temperature was 98.6 F., the pulse 116. The rigidity of the neck and tremor of muscles had disappeared. The reflexes were normal. There was no weakness and the child looked well.

*Oct. 15.*—There was slight fever and cough for a number of days subsequently, but there was complete recovery without paralysis.

CASE 968.—O. N., a girl, aged one year. (Patient of Dr. E. O. Ficke, Davenport, Iowa.)

*Sept. 18.*—Onset with restlessness, looseness of bowels, nausea, and abnormal drowsiness. 8 P. M.—The temperature was 103, the pulse 140. The child cried when handled and did not want to be moved. The knee-jerks were exaggerated, ataxia was marked, the head was retracted, and the neck stiff. 11 P. M.—There was marked trembling of the extremities, ataxia, the head was retracted, the neck was stiff, and the knee-jerks were exaggerated. The tonsils were large and moderately red and two follicles were filled with cheesy exudate. The larynx was diffusely hyperemic and there were palpable lymph-glands outside of either tonsil. Seven teeth were found to be in process of eruption. Spinal puncture was made; the fluid was under increased pressure and 1.5 c.c. were obtained. Cell count 40, globulin test +. Six c.c. of serum were given.

*Sept. 19, 10 P. M.*—The patient slept all night and appeared brighter in the morning. She had felt well all day, had been up playing until



about 5 o'clock. The tremor was absent and she walked without ataxia. The knee-jerks were normal. There was no weakness. Six c.c. of serum were given.

*Sept. 20.*—The temperature was normal. She looked well and was bright and active. No weakness was noted.

*Oct. 1.*—The temperature was normal and she was perfectly well, up and around, with no weakness.

*Oct. 15.*—The child was perfectly well.

(Temperature and pulse curves, Chart 1.)

CASE 971.—E. S., a girl, aged nine years. (Patient of Dr. A. B. Kuhl, Davenport, Iowa.)

*Sept. 19.*—Headache, nausea, and vomiting began two days previously and pain in the abdomen the day before. 4 P. M.—There were pain and stiffness in the back of the neck and the girl was drowsy. The knee-jerks were diminished. The Kernig sign was present. The temperature was 102 F., the pulse 130. The thyroid was enlarged; the tonsils were large, and three enlarged glands were noted outside either tonsil. There was no weakness. Spinal puncture was made, with spurting of fluid, and 15 c.c. were obtained. Cell count 8, globulin test +. Ten c.c. of serum were given.

*Sept. 20.*—The temperature and pulse were normal and she felt well, with no weakness.

*Sept. 21.*—The girl appeared perfectly well and there was no weakness.

*Oct. 15.*—Recovery was complete without paralysis.

CASE 972.—M. J., a girl, aged eight years; sister of Case 964. (Patient of Dr. A. Grassau, Princeton, Iowa.)

*Sept. 20.*—She complained of pain in the upper abdomen the day before. There was no fever in the morning but a temperature of 101 F. in the afternoon. She was extremely restless and had developed tremor of the muscles of the head and arms during the night. Stiffness of the neck and marked twitchings of the muscles were noted in the night. 10 A. M.—The tonsils were large and a large amount of peculiar pus was expressed from the left, and a small amount from the right. Two cervical glands were palpable on either side of the neck just outside of the tonsil. There were marked retraction and stiffness of the neck and back. Attempts to flex the head and the trunk caused severe pain. She was very tremulous and ataxic. The knee-jerks were markedly exaggerated. Kernig on both sides. The pupils were dilated and the thyroid was enlarged and soft. A spinal puncture was made with spurting of turbid fluid; 10 c.c. were obtained. Cell count 800, globulin test ++. Ten c.c. of serum were given. The muscle twitching was lessened immediately after the injection of the serum. 6 P. M.—The stiffness in the neck and the tremor had decreased.

*Sept. 21.*—The child looked brighter and the twitchings had dis-

appeared. There was less retraction of the head and the neck and back were not so stiff. No weakness was evident. The right knee-jerk was normal, the left slightly exaggerated. Kernig less marked. The temperature was 99.4 F., the pulse 130. A slight tremor of the muscles was noted under excitement while the serum was being injected. Ten c.c. of serum were given.

*Sept. 22.*—The girl looked brighter and no twitching of muscles was noted. The pupils were normal in size and the face was symmetric. She walked without dragging the foot and without ataxia. There was no weakness. The knee-jerks were normal. A spinal puncture was made; the fluid was under increased pressure and 2 c.c. were obtained. Cell count 500, globulin +. Six c.c. of serum were given.

*Sept. 23.*—She appeared well, the stiffness of the neck and back and the twitchings of the muscles had disappeared. No weakness was observed.

*Oct. 14.*—Recovery was complete without paralysis.

(Temperature and pulse curves, Chart 1.)

CASE 975.—J. N., a boy, aged five years. (Patient of Dr. L. F. Sullivan, Donahue, Iowa.)

*Sept. 21.*—He had had an attack of follicular tonsillitis two weeks previously, with a slight fever lasting for two days. He then seemed well until four days before the onset of the present illness, when he developed diarrhea, followed the next day by fever, severe headache, and vomiting. He was restless and nervous, with a temperature the night before of 104.4 F., and a pulse of 130. He had been drowsy the preceding day and was extremely restless during the night, having had a number of attacks of marked twitchings of the muscles of the extremities. 4.30 P. M.—There was doubtful weakness of the left hand, but otherwise no paralysis. The tonsils were large, and palpable glands were found on either side. He appeared abnormally drowsy, could be aroused, but fell asleep promptly. The head was retracted. Moderate Kernig. There was a definite stiffness of the neck. The right knee-jerk was exaggerated, the left obtainable only on reinforcement. The temperature was 102.4. A spinal puncture was made with spurting of fluid, and 10 c.c. were obtained. Cell count 83, globulin test +. Ten c.c. of serum were given.

*Sept. 22, 10 A. M.*—The knee-jerks were normal. No weakness was evident. The temperature was 99.8 F. Seven and one-half c.c. of serum were given.

*Sept. 23.*—He appeared well, the temperature was normal, and there was no weakness.

*Oct. 16.*—The child was perfectly well. There was slight dragging of the right foot for one week after he got up.

CASE 979.—E. S., a girl, aged four years. (Patient of Dr. F. O. Burk, Davenport, Iowa.)

*Sept. 24.*—The patient awoke at 2 o'clock in the morning with severe generalized tremors, a high fever, vomiting, and diarrhea. 11 A. M.—There was almost continuous tremor, with sudden spasms of the muscles of the extremities, face, neck, and eyes. The temperature was 103.8, the pulse extremely rapid. The girl lay in bed with head retracted and in a semicomatose condition, from which she could scarcely be aroused. There were repeated involuntary urinations and defecations, the stools were offensive and contained a large amount of mucus. The body was extremely hot, the extremities were cold, and the skin was alternately pale and flushed. A moderate cyanosis was present. The left knee-jerk was markedly exaggerated, the right absent. Bilateral Babinski and Kernig. The neck was stiff. The tonsils were large and large lymph-glands were noted on the left side; none on the right. Spinal puncture was made and 4 c.c. of fluid were obtained. Cell count 19, globulin test +. 12.15 P. M.—Eight c.c. of serum were given. 3.30 P. M.—The condition was decidedly better and the child could be aroused. The facial expression was less anxious, and she lay quiet. The temperature was 101. The right knee-jerk was obtainable, the left normal. Kernig absent. The stiffness of the neck was less marked. She slept quietly with only occasional twitchings of the muscles of the forearms. She had not had sudden spasms of muscles since the injection of the serum. Ten c.c. of serum were given. 9 P. M.—The picture was entirely changed. The child was bright and rested quietly. The tremors and spasms had disappeared, the knee-jerks were normal, and Babinski and Kernig signs were absent. The temperature was 99 F., the pulse 112.

*Sept. 25, 2 P. M.*—The temperature was normal, the pulse 108. The child was rational, looked perfectly well, and smiled. The pupils were equal, the tongue protruded in the median line, and the reflexes were normal. There was slight rigidity of the neck. There was no weakness.

*Oct. 15.*—Recovery was complete without paralysis.  
(Temperature and pulse curves, Chart 1.)

CASE 988.—C. L., a boy, aged eight years. (Patient of Dr. F. C. Skinner, Le Claire, Iowa.)

*Sept. 27.*—The patient had gone to bed feeling well, and awoke about 6 A. M. with headache, pain in the stomach, and vomiting. He did not vomit food, but material containing much mucus. The vomiting persisted and one loose bowel movement occurred. There was marked tremor over the whole body at 7 A. M. The temperature at 9 A. M. was 104, the pulse 160. 11.45 A. M.—He complained of headache, of stiffness of the neck, pain in the back of the neck, was apathetic and looked sick. There was tremor of the eyelids, the tongue was tremulous, and there was tremor of the extremities. The throat was diffusely hyperemic, the tonsils were large, and pus was expressed from the pole of the

left. The follicles were empty. Two large glands were palpable on the left side, just outside the tonsil; none on the right. The temperature was 104, the pulse 160. The knee-jerks were increased. Kernig absent. The neck was held rigid. A spinal puncture was made; the fluid was clear and under moderate pressure. Cell count 8, globulin test weakly positive. Ten c.c. of serum were given. 11.30 P. M.—He looked brighter. The temperature was 104, the pulse 120. Ten c.c. of serum were given.

*Sept. 28.*—The temperature was 100, the pulse 96. The stiffness of the neck had disappeared. He felt much better and there was no weakness.

*Sept. 29, 9 P. M.*—The temperature was 98.6, the pulse 74. The boy felt well and there was no weakness.

*Oct. 15.*—There was complete recovery without paralysis.

(Temperature and pulse curves, Chart 1.)

CASE 996.—E. B., a girl, aged six years. (Patient of Dr. W. H. Rendleman, Davenport, Iowa.)

*Sept. 28.*—The patient went to bed apparently perfectly well the night before and got up in the morning with pain in the stomach. She vomited at noon and diarrhea began in the afternoon; the stools had a very foul odor. She was drowsy and sleepy all day; could be aroused, but went to sleep immediately. The temperature was 101.4, the pulse 130. She complained of headache in the morning and there were marked twitchings of the muscles at intervals, especially of the shoulder. 7 P. M.—The face was flushed, the head retracted, and there were twitchings of the muscles. She had cramps in the stomach, followed by a bowel movement. The tonsils were large and diffusely red. There was considerable secretion in the throat. A lymph-gland was noted on the left side. The left knee-jerk was normal, the right absent. There was moderate distention of the abdomen. The temperature was 102.4, the pulse 144. A spinal puncture was made, with spurting of fluid, and 10 c.c. were obtained. Cell count 22, globulin test +. Ten c.c. of serum were given.

*Sept. 29.*—The temperature was 98.6, the pulse 110. The girl felt well and was up and dressed.

*Oct. 2.*—There had been severe cramps two days before, followed by two large bowel movements containing blood; none had occurred since. The reflexes, temperature, and pulse were normal. There was no weakness.

*Oct. 7.*—There was complete recovery without paralysis.

(Temperature and pulse curves, Chart 1.)

## RESULTS

GROUP 1.—*Patients showing no paralysis at the time of the serum treatment.* The 16 patients in this group recovered without paralysis

TABLE 1.—SUMMARY OF CASES SHOWING NO

CASE No.	SEX	AGE, YEARS	CONDITION OF PATIENT	SPINAL FLUID		
				Amount With-drawn, C.c.	Cell Count	Globu-lin
936	M	9	Irritable, nervous, retraction of head, exaggerated reflexes	15	60	+
944	M	11	Rigidity of neck and back. Left knee-jerk diminished, right exaggerated	15	16	+
950	F	2	Drowsy, retraction of head, neck stiff, twitching of muscles, tremulous	20	133	++
953	M	3	Drowsy, rigidity of neck, bilateral Kernig, twitching of muscles	10	18	+
954	M	9	Rigidity of neck, right knee-jerk exaggerated, left diminished, double Kernig	3	11	+
956	M	5	Double Kernig, tremulous, twitchings of muscles	10	44	+
962	F	24	Headache, pain in back, marked general weakness, rigidity of neck, knee-jerk weak	20	23	++
964	F	4	Mental apathy, double Kernig and Babinski, hyperesthesia, tremulous, twitchings of muscles	10	211	+
966	M	3.5	Retraction of head, tremor of muscles, ataxia, right knee-jerk diminished, left exaggerated	12	27	+-
968	F	1	Retraction of head, rigidity of neck, knee-jerks exaggerated, ataxia	1.5	40	+
971	F	9	Apathy, back and neck rigid. Double Kernig	15	8	+
972	F	8	Marked rigidity of neck and back. Tremulous and ataxic. Double Kernig	10	800	++
975	M	3	Rigidity of neck. Right knee-jerk exaggerated, left weak	10	83	+
979	F	4	Marked generalized tremor of muscles. Retraction of head. Semi-comatose. Left knee-jerk exaggerated, right absent	4	19	+
988	M	8	Rigidity of neck and back. Tremor of muscles of eyelids and extremities	8	8	+
996	F	6	Retraction of head. Twitchings of muscles. Right knee-jerk absent	10	22	+

(Table 1). One of these (Case 975), in which the serum treatment was begun on the fourth day, dragged the right foot for one week, but since the patient was not asked to walk on account of the severity of the symptoms, this may have been present at the time the serum was given.

The ages of the patients in this group ranged from one to twenty-four years, the average being seven years. Eight were males and 8 females. The spinal fluid was under increased pressure in all; in 2 it was distinctly turbid, and in the others clear. The amount withdrawn ranged from 1.5 to 20 c.c., the average being 11 c.c. The cell count ranged from 8 to 800 per cubic millimeter, the average being 95. The globulin content was increased in all. The temperature was relatively high at the time of the first injection (Table 1). In 4 patients it was between 101 and 102; in 8 between 102 and 103; in 4 between 103 and 104. The pulse was very rapid in practically all.

The serum treatment was begun on the first day in 7 patients, on the second day in 2, on the third day in 5, and on the fourth day in 2.

## PARALYSIS AT THE TIME OF SERUM TREATMENT

DAY OF DISEASE	TEMPERATURE AT TIME OF TREATMENT	TOTAL AMOUNT OF SERUM GIVEN, C.C.	RESULT
2	101	10	Temperature dropped by crisis. Prompt recovery without paralysis
3	104	12	Recovery without paralysis
3	101.5	6	Temperature disappeared by crisis. Prompt recovery without paralysis
1	101.5	10	Temperature dropped by crisis. Prompt recovery without paralysis
4	103	17	Temperature dropped by crisis. Prompt recovery without paralysis. Attack of appendicitis four days later
1	103	15	Temperature dropped by crisis. Complete recovery without paralysis in twenty-four hours
1	103.5	12.5	Temperature dropped by crisis. Prompt recovery without paralysis
3	103	26	Complete recovery without paralysis
3	103	17.5	Prompt recovery without paralysis
1	103	12	Prompt recovery without paralysis
3	102	10	Prompt disappearance of temperature. Recovery without paralysis
2	102.5	26	Recovery without paralysis
4	102.4	17.5	Critical drop in temperature. Slight dragging of right foot for one week. Complete recovery
1	103.8	18	Temperature dropped by crisis. Marked improvement in three hours. Complete recovery without paralysis
1	104	20	Temperature dropped by crisis. Complete recovery without paralysis in twenty-four hours
1	102.4	10	Temperature dropped by crisis. Complete recovery without paralysis in twenty-four hours

One dose only was given in 7 patients, two in 7, and three in 2. The amounts given ranged from 6 to 26 c.c., the average being 15 c.c. A prompt drop in the temperature and the pulse-rate occurred in nearly every instance when invasion of the central nervous system, as manifested by the cell count in the spinal fluid, was not too great, quite irrespective of the previous duration of symptoms (Chart 1). The drop in temperature occurred without an initial rise. The symptoms often disappeared in an astonishingly short time. Improvement began in some instances while the serum was being slowly injected or soon thereafter. A restless, sleepless, hyperesthetic child would often fall asleep soon after the administration of the serum. Twitchings and tremor of the muscles often became less or disappeared within a few hours after giving the serum. In 7 patients the temperature dropped to normal and the symptoms practically disappeared within twenty-four hours; in 7 they disappeared within forty-eight hours, and in 2 within seventy-two hours (Chart 1).

## CASES SHOWING SLIGHT PARALYSIS AT THE TIME OF SERUM TREATMENT

CASE 939.—G. R., a boy, aged seven years. (Patient of Dr. H. M. Decker, Davenport, Iowa.) The boy had had meningitis at seven months, and three or four attacks of pneumonia. He had been well for sixteen months, although not very strong.

*Aug. 29.*—He was listless; played at intervals and was constipated.

*Aug. 30.*—The listlessness increased and he lay around. He was constipated and vomited in the evening.

*Aug. 31.*—Very listless; he slept most of the time and was still constipated. There was no apparent fever or pain.

*Sept. 1.*—He was in a semicomatose condition, was awakened with difficulty, and could not be kept awake to answer questions. The temperature was 102, the pulse 100, the reflexes and strength were normal. There was moderate distention of the abdomen, the throat was faintly reddened, and the tonsils were normal in size. There was no glandular enlargement, cough, or coryza.

*Sept. 2.*—The temperature was 101.8, the pulse 90, otherwise the condition the same as the day before. *8 A. M.*—Condition the same, semicomatose, the neck held rigid, and attempts to flex the head caused pain. The temperature was 102, the pulse 100. The speech was stuttering and he had hallucinations. *3 P. M.*—Condition much the same. He complained of pain in the region of the right ear and the mastoid. The reflexes were normal, the strength was good, the throat was somewhat reddened. No pus could be expressed from the tonsils; one lymph-gland outside the right tonsil was enlarged. The child was mentally confused and could scarcely be aroused. There was no weakness. *6 P. M.*—The mental condition was growing worse; there was weakness of the right angle of the mouth. The temperature was 101, the pulse 100. A lumbar puncture was made and 0.3 c.c. of fluid obtained; a moderate amount escaped through the line of puncture after the needle was withdrawn. Cell count 78, globulin test +. Seven and one-half c.c. of serum were given.

*Sept. 3, 7.30 A. M.*—The temperature was 98, the pulse 72. The child was quiet and ate a bowl of oatmeal with relish. He was mentally clear but still somewhat sluggish. There was no extension of paralysis. *1 P. M.*—He was mentally brighter.

*Sept. 4, 7 A. M.*—He was mentally normal and slept well; there was no extension of the paralysis. He had no pain anywhere and walked normally. The weakness of the right angle of the mouth was less marked.

*Sept. 5.*—There was slight weakness of the right corner of the mouth; otherwise he was normal.

*Oct. 15.*—The recovery was complete.

(Temperature and pulse curves, Chart 2.)

CASE 940.—B. B., a girl, aged ten months. (Patient of Dr. F. Neufeld, Davenport, Iowa.)

*Sept. 4.*—The child was fussy and feverish the day before. There was fever, restlessness, and twitching of the muscles of the hands and face in the night. During the forenoon the temperature was 105.2, the pulse 180. The bowels were flushed. By noon there were twitchings of the muscles of the face and arms bordering on slight convulsive attacks. *9.30 P. M.*—The temperature was 104. There was twitching of the muscles of the face and fingers, the head was retracted, the eyes turned back, and attempts to flex the head caused the child to cry out. There was doubtful weakness of the muscles of the right angle of the mouth. The stools contained a large amount of greenish mucus. A spinal puncture was made, with spurting of fluid. Ten c.c. of slightly

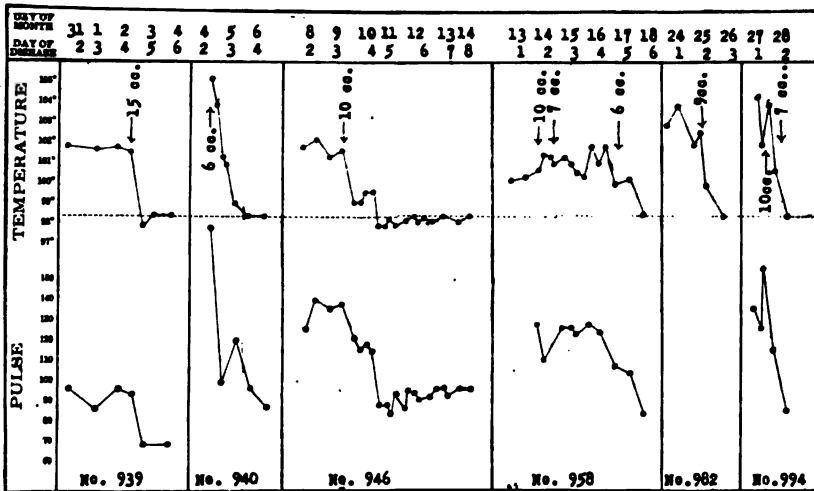


Chart 2.—Temperature and pulse curves of patients showing slight paralysis at the time of serum treatment.

cloudy fluid were withdrawn. Cell count 155, globulin test +. Six c.c. of serum were given. *11.30 P. M.*—The bowels were flushed with sodium bicarbonate and salt solution.

*Sept. 5, 7 A. M.*—The temperature was 101.5, the pulse 104. The child appeared brighter; had slept most of the night. There was still slight retraction of the head and stiffness of the neck. *11 A. M.*—The temperature was 101, the pulse 125. The child slept quietly; there was no retraction of the head, no weakness anywhere. The stools were greenish and contained undigested milk-curds. Five c.c. of serum were given.

*Sept. 6.*—The child appeared well in every respect. She laughed and kicked vigorously with both legs. The weakness of the right side of the mouth had disappeared.



*Oct. 15.*—Recovery was complete.  
(Temperature and pulse curves, Chart 2.)

CASE 946.—F. C., a boy, aged five years. (Patient of Dr. F. Lambach, Davenport, Iowa.)

*Sept. 9.*—The boy complained of headache two days before and was feverish. The symptoms were thought to be due to enlarged tonsils, and arrangements were made for their removal. During the night a high fever developed.

*Sept. 10.*—He vomited twice during the day and was unusually sleepy. The tonsils became more enlarged, and pus was expressed from the left. There were several enlarged lymph-glands outside the left tonsil; none on the right side. There was marked tremor of the muscles of the jaw, noted especially on examining the throat. There were peculiar jerky movements of the muscles of the hands and about the eyes. The child walked normally. There was no evident weakness and no stiffness of the neck. The temperature was 102.5, the pulse 130. *10 P. M.*—The child had been flighty and nervous during the day and very drowsy. He slept most of the day with the mouth open, the eyes partly closed, and the head retracted. He could be aroused but would fall back to semicomatose sleep immediately. The head was retracted and the neck stiff. There were Kernig and Babinski signs on both sides; the left knee-jerk was absent and the right sluggish. There was marked ataxia in walking and the left foot dragged. There were peculiar jerky movements of the arms, and some difficulty in swallowing. He was unable to raise the eyelids normally, especially the left. The temperature was 101.5. *10.30 P. M.*—A spinal puncture was made; the fluid was under pressure and 15 c.c. were obtained. Cell count 18, globulin test ++. White blood count 10,000. The listlessness and inability to keep awake continued for one-half hour after spinal fluid was withdrawn. *11 P. M.*—Ten c.c. of serum were given. *11.15 P. M.*—The child had brightened up, took an interest in things, and talked for fully half an hour. In puckering his mouth attempting to whistle and in showing his teeth it was noticed that the left side of the face was partially paralyzed.

*Sept. 11.*—He had slept quietly all night and appeared bright. The rigidity of the neck was less marked. Kernig and Babinski signs were absent on both sides. The knee-jerk on the right side was normal; on the left side a number of vigorous kicks were obtained. The child walked without dragging the left foot. He opened his eyes normally, but there was still slight weakness of the left side of the face when he attempted to whistle, but less marked than the night before. The temperature was 99.2. White blood count 11,800.

*Sept. 12.*—The temperature was 98, the pulse 90. He felt perfectly well; all weakness of the muscles, including those of the left side of the face, had disappeared.

*Oct. 15.*—Complete restoration of muscle function.  
(Temperature and pulse curves, Chart 2.)

CASE 947.—H. L., a male, aged twenty years. (Patient of Dr. F. E. Rudolf, Davenport, Iowa.)

*Sept. 10.*—Two days previously he noticed a peculiar uncontrollable tremor of the hands, at times approaching spasms. He had no appetite, was nauseated, but did not vomit, and was constipated. He slept poorly the night before, was extremely nervous, and tossed about. He had repeated attacks of tremor and twitching of the muscles of various parts of the body. There had been severe headache the day before and tremor of the muscles. In the morning he noticed a peculiar thickness of the tongue and he was unable to swallow toast, but could wash it down with liquids. *1 P. M.*—While in the doctor's office he was very drowsy; said his tongue felt thick and tended to go to the roof of the mouth when swallowing. He was extremely restless and nervous; the muscles of various parts of the body, especially the right arm and leg, and the lips, twitched markedly at short intervals. He was ordered to go home to bed. *3.30 P. M.*—While the history was being taken the patient dropped off repeatedly into partial sleep. He complained of headache and of feeling very nervous. There was twitching of the muscles of the right arm and leg and the lips at short intervals. The temperature was 99.8, the pulse 96. White blood count 8700. The tonsils were large, and cheesy material was expressed from both. The muscles of the tongue were weak. There was slight rigidity of the neck and ataxia. The right knee-jerk was exaggerated, the left normal. He was unable to swallow toast. *4 P. M.*—A spinal puncture was made; the fluid was under pressure and 35 c.c. were withdrawn. Cell count 9, globulin test + +. *4.20 P. M.*—No relief from the headache; twitching of the muscles continued. Twenty-two c.c. of serum were injected intravenously. While the injection was being made the patient stated with some surprise that his headache had disappeared and that he felt very much better. The twitchings of the muscles disappeared also before the injection of the serum was completed. *5 P. M.*—The twitching of the muscles had not returned; the thickness of the tongue was less marked. The patient, much to his astonishment, was able to swallow toast.

*Sept. 11, 9.30 A. M.*—The headache and jerking of muscles had not returned. The thickness of the tongue had disappeared completely by 6 P. M. the night before. There was not the slightest difficulty in swallowing, the stiffness of the neck had disappeared, the temperature was normal, and the pulse 78. White blood count 9000. The patient stood erect and walked without ataxia. There was no weakness, the knee-jerks were equal and normal, the face was symmetric. He begged for something to eat and insisted that he was perfectly well.

*Oct. 15.*—Urticaria six days after giving the serum. Recovery was complete.

This patient had had diphtheria antitoxin thirteen years previously. He recovered without paralysis and with only slight serum disease.

CASE 951.—L. R., a male, aged twenty-three years, employed as a truck driver. (Patient of Dr. D. G. Kreul, Davenport, Iowa.)

*Sept. 12.*—The patient had contracted a cold five days before. He sneezed, the nose was congested, and there was much discharge the first two days. At that time there was soreness of the throat and slight fever. He had had diarrhea two days previously. The present illness began the afternoon before; the patient felt achy and nervous; his head ached and he began to have attacks of twitching of the muscles in various parts of the body. An intense headache developed suddenly the next morning while he was on the way to work. Two hours later he vomited, was unable to walk, and had to lie down. The jerking of the muscles became much worse. He was taken home and put to bed. *2 P. M.*—He complained of severe headache, nausea, tightness in the chest, and dry cough. The tonsils were large and red; no attempt was made to express pus. There was a tender gland just outside the right tonsil, and several palpable glands on the left side. The patient lay in bed with a peculiar expression of tension on his face. He appeared nervous, and marked twitchings occurred, at short intervals, of muscles of various parts of the body, especially of the left arm. The right knee-jerk was exaggerated, the left barely obtainable, and only on reinforcement. There was weakness in the legs, especially the left; the gait was ataxic. There was marked weakness in the extension of the left hand, none of the right. The temperature was 99.6. A spinal puncture was made, with spurting of fluid, and 30 c.c. were obtained. Cell count 18, globulin test +. No relief followed the spinal puncture. Twenty c.c. of serum were given.

*Sept. 13.*—The nurse said that he had had only two jerking spells after the injection of the serum. He had been restless during the first part of the night, but had slept well and quietly during the latter part. In the morning he felt like getting up and going to work. He looked well. The knee-jerks on both sides were normal. The cough persisted. The extension of the left wrist was powerful; the weakness of the left leg had disappeared; there was no weakness. The temperature was normal. Twelve c.c. of serum were given.

*Sept. 14.*—The patient appeared perfectly well.

*Oct. 14.*—Recovery was complete.

CASE 952.—M. D., a girl, aged fifteen months. (Patient of Dr. T. D. Starbuck, Davenport, Iowa.)

*Sept. 12.*—The child had been irritable and fussy and had had diarrhea for two weeks. She had vomited at intervals the day before and during the morning. There was apparently no fever until the night before. At midnight severe convulsions occurred, and during the morning there were nine convulsions which had to be controlled with ether. A drawn condition of the left side of the face was noted. A cough had existed for two days, associated with râles in the chest. She did not want

to be handled. 3.45 P. M.—The temperature was 103. The muscles of the right hand twitched, and there was weakness of the muscles of the left side of the face and the left eyelid. The head was retracted, and attempts to flex it caused pain. The knee-jerks were exaggerated. Babinski's sign was present. A spinal puncture was made; the pressure was increased, and 10 c.c. of fluid obtained. Cell count 22, globulin test ++. Six c.c. of serum were given.

Sept. 13.—The child had had no convulsions since the injection of the serum. The highest temperature was 99.2. She appeared bright and the weakness of the left side of the face and the left eyelid was less marked.

Sept. 14.—She appeared perfectly well. Her temperature was normal and she walked normally. The weakness of the left side of the face and the left eyelid was less marked.

CASE 958.—T. D., a boy, aged five years. (Patient of Dr. E. F. Strohbehn, Davenport, Iowa.)

Sept. 14.—The child was perfectly well until 2 o'clock two nights before, when he became restless and feverish. He vomited repeatedly in the morning, the vomitus containing a large amount of mucus but no blood. There was no diarrhea. He complained of severe headache. He seemed very drowsy and talked constantly in his sleep during the night. He complained of pain in the small of the back, and in the morning showed twitchings of various muscles of the body, with severe pain in the back. There was no rigidity of the neck during night or morning. The temperature in the night was 100.6; in the morning it was 100.4. 11.30 A. M.—He was restless, and lay with head retracted. There was twitching of the muscles of the hands and of the legs. The face was flushed, the neck stiff, and the child was unable to bring chin to chest. Flexion of the head caused pain in the neck and back. Kernig +. The knee-jerks were exaggerated. The temperature was 101.4, the pulse 112. There was weakness in the extensors of the right leg; no other weaknesses could be detected. The tonsils were large, the throat hyperemic and moist, and there was a palpable lymph-gland on either side of the neck, just outside the tonsil. 11.45 A. M.—A spinal puncture was made; the fluid was under pressure and slightly turbid, and 10 c.c. were obtained. Cell count 141, globulin test ++. Ten c.c. of serum were given. Ten minutes after the injection was finished the boy said his headache had disappeared. 6 P. M.—The temperature was 101.4, the pulse 130. The back was rigid, the left knee-jerk was normal, the right diminished. There was no increase in weakness of the right leg, and no weakness otherwise. 10 P. M.—The temperature was 101.2, the pulse 130. There were slight twitchings of the muscles of the mouth, the eyelids, and the arms, and less rigidity of the neck. The left knee-jerk was exaggerated, the right diminished. Seven and one-half c.c. of serum were given.

*Sept. 15, 1.40 P. M.*—The child looked well. There was less twitching of the muscles about the mouth and eyes, the face was symmetric and less flushed. The increase in the weakness of the right leg was moderate, and he was able to raise the leg in extended position.

*Sept. 17, 12 M.*—The temperature was 100.4. The weakness in the right leg had increased and he was unable to lift his foot from the bed in the extended position, but could move his toes. The extensors of the right foot were unimpaired. Six c.c. of serum were given.

*Sept. 18.*—The temperature was normal. There was a slight stiffness of the neck; the right knee-jerk was absent. There was definite improvement in muscle power in the right leg and in the back and no weakness otherwise.

*Oct. 15.*—There was slight weakness in the right thigh and in the back which was decreasing rapidly.

(Temperature and pulse curves, Chart 2.)

CASE 961.—H. B., a girl, aged eleven months. (Patient of Dr. H. M. Decker, Davenport, Iowa.)

*Sept. 15.*—The child had been well until three days before when she developed fever and began to vomit. There was no bowel disturbance and the fever continued. She had been abnormally drowsy since the onset. The temperature was 102 (the morning of Sept. 15) and for the first time it was noticed that the child was unable to hold her head up when sitting up. *3 P. M.*—The tonsils were small, and no attempt was made to express pus. There were two small lymph-glands on the right side of the neck just outside the tonsil. The left side of the face drooped. A marked weakness of the muscles of the neck and undoubted difficulty in swallowing were noted. The voice was weak. A spinal puncture was made; the fluid was under pressure and 10 c.c. were obtained. Cell count 130, globulin test +. Five c.c. of serum were given.

*Sept. 16.*—The temperature was normal; the child appeared well. There was marked improvement in the muscles of the neck and the right side of the face.

*Oct. 15.*—Complete restoration of muscle function.

CASE 969.—L. M., a girl, aged two years. (Patient of Dr. A. Grassau, Princeton, Iowa.)

*Sept. 19.*—The child had contracted a cold and had had a severe cough four days previously. There was a high fever the following night, apparently none the next night, and again a high fever the night of the eighteenth; there was looseness of the bowels and vomiting. *4.30 A. M.*—The temperature was 104.5. The patient was tremulous and had a number of attacks in which the muscles of various parts of the body, particularly of the face, jerked. *5.30 A. M.*—Severe generalized clonic and then tonic convulsions occurred, which had to be controlled with chloroform and opiates. *10 A. M.*—The temperature was 102. She had a severe cough, was extremely tremulous, with the knee-jerks on

the right side exaggerated and on the left side weak. Undoubted weakness in the left leg was noted. There was paralysis of the internal recti; both eyes turned out sharply. The head was retracted, the neck was very stiff, and the right side of the face was partially paralyzed. There was marked Kernig. Coarse mucous râles were detected in various parts of the chest. A spinal puncture was made, with spurting of clear fluid, and 8 c.c. were obtained. Cell count 17, globulin test +. Ten c.c. of serum were given. Shortly after the injection of serum the tremor of the muscles of the extremities disappeared, and the child slept naturally. 8 P. M.—She seemed better. The twitchings were less marked and there were no spasms. The temperature was 102.

Sept. 20, 9 A. M.—The patient was brighter and active. There were still twitchings of the muscles but no spasms. She moved her arms and legs actively and walked without tremor. The temperature was 100. The rigidity of the neck and the strabismus had disappeared. A slight drawn condition of the right side of the face was still present but less marked than the day before. Five c.c. of serum were given.

Sept. 21.—The general condition was much better. Twitchings of muscles had not occurred following the injection of serum the day before. There was no weakness of the muscles of the extremities. The head was held erect; she sat up without difficulty. Coarse mucous râles in the chest, especially over the right side, could be detected. The temperature was 102.4.

Sept. 22.—The temperature was normal. There was no weakness.

Oct. 14.—Recovery was complete.

CASE 970.—A. M., a boy, aged seventeen months. (Patient of Dr. H. U. Braunlich, Davenport, Iowa.)

Sept. 19.—Two weeks previously the child had had diarrhea with mucus in the stools for a week. He was apparently well until four days before (Sept. 15), when he developed a high fever and extreme restlessness. The next day he vomited, and on the next was abnormally sleepy, with twitchings of the muscles of the face and the extremities. Temperature 102. 2 P. M.—The tonsils were normal in size, but a small amount of pus was expressed from the right. There was an enlarged gland outside the right tonsil, but not on the left side. The throat was red, the muscles of the tongue weak, and the head retracted. He appeared markedly apathetic. His eyes were rolled back and he cried out at intervals as if in pain. There was marked weakness of the muscles of the neck, the right side of the face, and the tongue. He could move his extremities but was unable to stand. Knee-jerks were absent. There was marked Kernig. The temperature was 100.6. A spinal puncture was made, the fluid was under pressure, and 10 c.c. were withdrawn. Cell count 194, globulin test +. Ten c.c. of serum were given.

Sept. 20.—The temperature was normal, the child appeared brighter; there was no extension of the paralysis.

*Sept. 21.*—There was no extension of the paralysis and an undoubted improvement on the right side of the face.

*Sept. 23.*—Marked improvement was shown in the power of the muscles of the legs, neck, and right side of the face.

*Oct. 15.*—Complete recovery of muscle function.

CASE 974.—H. A., a girl, aged eight years. (Patient of Dr. J. P. Comegys, Rock Island, Illinois.)

*Sept. 20.*—The girl had been perfectly well until two days before, when she suddenly became extremely ill, with persistent vomiting, marked diarrhea, and high fever. She vomited or attempted to vomit almost constantly during the first night and had numerous extremely offensive bowel movements which contained a large amount of mucus. The diarrhea continued after the administration of castor oil, and many movements containing greenish mucus and pus-like material mixed with blood had occurred the day before. Pain developed in the back of the neck and she was very shaky. 6 P. M.—The child appeared to be sick. There were marked tenesmus and numerous bowel movements containing a large amount of mucus and bloody pus. The eyes were sunken, the lips and tongue red. The head was retracted and attempts to flex the head and the neck caused pain. Kernig sign present. The knee-jerks were markedly exaggerated. Weakness of the muscles of the right side of the face was noted. The tonsils were normal in size; the throat hyperemic and covered with mucus. A spinal puncture was made, the fluid was under moderate pressure, and 10 c.c. were obtained. Cell count 44, globulin test +. Ten c.c. of serum were given. Fifteen minutes after the injection the knee-jerks became normal on repeated tests.

*Sept. 21.*—There was no extension of paralysis. The drawn condition of the right side of the face was barely noticeable. The bowel condition was unchanged.

*Oct. 16.*—Recovery was complete.

CASE 981.—C. R., a girl, aged eight months. (Patient of Dr. Neufeld, Davenport, Iowa.)

*Sept. 25.*—The infant was weak and poorly nourished. She had had diarrhea one week previously, and fifty-six hours previously had become ill and feverish, with general irritability and restlessness. She had a number of spells in which she shook. She lay in bed, was extremely restless, and the head was retracted. 10.30 A. M.—She was apathetic and lay with head retracted. She cried at attempts to flex the head. There was marked tremor of the hands, at times approaching convulsive spasms. The knee-jerks were exaggerated. There seemed to be some weakness in the extensors of the hands. The temperature was 102.8. A spinal puncture was made, the fluid spurted and was definitely turbid; 2 c.c. were obtained. Cell count 475, globulin test + + +. Seven c.c. of serum were given. 5.30 P. M.—She looked brighter and had

taken nourishment. The temperature was 102. She had been much quieter, more contented, and had played most of the afternoon. 7.30 P. M.—The temperature was 100. She appeared to be feeling better. 9.30 P. M.—Sleeping normally without twitchings.

Sept. 26, 10.15 A. M.—The temperature was 100. She looked bright and playful and smiled. Her face was symmetric; the reflexes were normal, and only slight rigidity of the neck was noted. No weakness. Five c.c. of serum were given.

Sept. 27.—Temperature and pulse normal. No weakness. The child appeared well.

Oct. 15.—Recovery was complete.

CASE 977.—G. S., a girl, aged two years. (Patient of Dr. F. C. Skinner, Le Claire, Iowa.)

Sept. 23.—The child had had coryza and sore throat five days previously. One sister, a hired man, and the father had had similar attacks. She vomited two nights before. The temperature was 102. She became drowsy the following day, with severe spasm and twitchings of muscles at midnight. 12.30 P. M.—There was slight rigidity of the neck. The left knee-jerk was exaggerated, the right diminished, and the right foot dragged slightly. The right eyelid drooped, and a weakness of the muscles of the right side of the face was apparent on crying. The throat was moist. The tonsils were large and there was an enlarged lymph-gland on either side, just outside the tonsil. The temperature was 100.4, the pulse 112. A spinal puncture was made, with spouting of fluid, and 10 c.c. were obtained. Cell count 83, globulin test +. Six c.c. of serum were given.

Sept. 24.—The temperature was normal, the pulse 80. The drawn condition of the face and the weakness of the right foot had disappeared.

Oct. 15.—Recovery was complete.

CASE 982.—H. R., a boy, aged three years. (Patient of Dr. James Dunn, Davenport, Iowa.)

Sept. 25.—Two nights previously the child had vomited repeatedly. Twitchings of the muscles had occurred the following day, and in the night he had diarrhea with stools of foul odor and containing a large amount of mucus. He had a severe convulsion in the night lasting twenty minutes, and in the morning was stuporous. The temperature was 102. There were frequent movements of the bowels, containing much greenish mucus, but no blood. 11.45 A. M.—The child was extremely apathetic and the head was retracted. He could be aroused but would fall asleep immediately. The muscles twitched. The tonsils were large and there was much mucus in the throat. Pus was expressed from the left tonsil, but none from the right. There were a number of enlarged glands on the left side adjacent to the tonsil, but none on the right. The knee-jerk on the left side was increased, on the right side, diminished. There was decided weakness of the muscles of the right



side of the face. A spinal puncture was made, the fluid was under pressure, and 12 c.c. were obtained. Cell count 25, globulin test +. Nine c.c. of serum were given. 6 P. M.—The temperature was 100. The child had rested quietly during the afternoon: he seemed brighter and talked. There was no change in the weakness of the right side of the face, and no weakness otherwise.

*Sept. 26, 7.30 P. M.*—He appeared well and bright and was hungry. The looseness of the bowels continued. The temperature was 98.6. There were no twitchings and the knee-jerks were normal.

*Sept. 28.*—The weakness of the right side of the face was absent; there was no other weakness. The bowel movements continued to contain a small amount of mucus. The temperature and pulse were normal.

*Oct. 15.*—Recovery was complete.

(Temperature and pulse curves, Chart 2.)

CASE 986.—M. P., a girl, aged five months. (Patient of Dr. J. W. Shields, Moline, Illinois.)

*Sept. 26.*—The child had had a discharge from the nose five days previously, but otherwise seemed well until midnight, when she had developed a high fever. The temperature at 6 A. M. was 102.2; at 8 A. M., 103.2. She vomited during the afternoon and was unusually drowsy. 5.30 P. M.—The tonsils were normal, the throat hyperemic and moist. The head was retracted, the neck stiff. Kernig sign present. The knee-jerks were exaggerated and there was a doubtful weakness of the right arm. The right eye turned in at intervals. A spinal puncture was attempted, but no fluid was obtained. Five c.c. of serum were given.

*Sept. 27.*—The temperature was normal. The slight weakness in the right arm and the right eye had disappeared. The child was apparently well in every respect.

*Oct. 15.*—Recovery was complete.

CASE 994.—L. A., a girl, aged four years. (Patient of Dr. A. E. Williams, Rock Island, Illinois.)

*Sept. 27.*—The child had apparently been perfectly well until noon, when she went to her mother asking to be held. She acted rather strangely, was extremely nervous, and complained of pain in her throat. During the afternoon she complained of pain in her left foot. 2 P. M.—The temperature was 104.4, the pulse 140 to 160. 5 P. M.—She vomited, was very drowsy and apathetic, but restless and extremely ill. 6 P. M.—The temperature was 102, the pulse 138. She was extremely apathetic and could scarcely be aroused. The head was retracted, the eyes rolled back, and there was a tremor of the muscles over the entire body. 9.30 P. M.—A generalized convulsion occurred, with involuntary urination and defecation. She was alternately flushed and pale. 10 P. M.—The temperature was 104, the pulse, 160. She was cyanotic, and the

twitchings of the muscles of the face, hands, and legs were severe. She became comatose and could not be aroused. There was weakness of the muscles of the right side of the face. The knee-jerks were exaggerated, the head retracted, and the neck stiff. Kernig and Babinski signs were marked. Spinal puncture was made, with spurting of the fluid, and 10 c.c. were obtained. Cell count 19, globulin test +. Ten c.c. of serum were given. The twitchings disappeared during the injection of serum.

*Sept. 28, 7 A. M.*—She slept quietly for two hours after the serum was given, but grew restless again and had a second convulsion at 3 o'clock. The tremors returned, lasted for an hour, and then gradually disappeared. The temperature was 100.8, the pulse 120. The twitching of the hands was slight. She looked brighter. The weakness of the right side of the face had disappeared and there was no other weakness. *1 P. M.*—Her color was good, she was active and begged for something to eat. She looked well. The knee-jerks were normal. Kernig and Babinski signs were absent. There were no twitchings of any of the muscles. The temperature was 98.6, the pulse 88. There was no weakness. Seven and one-half c.c. of serum were given.

*Sept. 29.*—The child was perfectly well.

*Oct. 15.*—Urticaria three days after the serum treatment, and a slight edema of the eyelids ten days later. Recovery was complete.

(Temperature and pulse curves, Chart 2.)

**CASE 1000.**—R. P., a boy, aged three years. (Patient of Dr. E. W. Bittner, Wheatland, Iowa.)

*Sept. 28.*—He complained of pain in his stomach. His head had ached four days before and since then he had been feverish. There was a marked twitching of the muscles when he was asleep. He was unusually drowsy and lay with head retracted. The temperature was 101, the pulse rapid. Paralysis of the left side of the face began the day before. *10 P. M.*—The paralysis of the left side of the face was almost complete and the weakness of the muscles of the neck was marked. His head would fall backward in bringing him to a sitting position. Strabismus was marked, and there was alternate flushing and pallor of the skin. He was extremely fretful and irritable. Ataxia was marked and the knee-jerks were exaggerated. He was unable to shut the left eye. Spinal puncture was made; the fluid was under pressure and distinctly turbid, and 5 c.c. were obtained. Cell count 955, globulin test + +. Ten c.c. of serum were given.

*Sept. 30, 4 P. M.*—The parents stated that the boy became quieter soon after the injection of serum, and rested quietly during the night. He appeared brighter in the morning. The muscles of the right side of the face were stronger, which was especially noticeable when he laughed and cried. The temperature was normal, the pulse 85. The muscles of the neck were decidedly stronger. He could hold his head

TABLE 2.—SUMMARY OF CASES SHOWING SLIGHT

CASE No.	SEX	AGE, YEARS	CONDITION OF PATIENT	SPINAL FLUID		
				Amount With-drawn, C.c.	Cell Count	Globu- lin
939	M	7	Stuporous, rigidity of neck, stuttering speech and hallucinations, weakness of right side of face	0.3	78	+
940	F	10/12	Twitching of muscles of face and fingers, weakness of right angle of mouth	10	155	+
946	M	5	Retraction of head, rigidity of neck, Kernig and Babinski both sides, left knee-jerk absent, ataxia, weakness of left foot, eyelids, and left side of face	15	18	++
947	M	20	Twitching of muscles, weakness of muscles of deglutition and tongue, inability to swallow solids, headache	35	9	++
951	M	28	Headache, muscular twitching, right knee-jerk exaggerated, left diminished, ataxia, weakness of left leg and arm	30	18	+
952	F	1 3/12	Twitching of muscles, rigidity of neck, weakness of muscles of left side of face	10	22	++
958	M	5	Rigidity of neck, double Kernig, muscular twitchings, weakness of extensors of right leg	10	141	++
961	F	1 1/12	Weakness of left side of face and muscles of neck. Slight difficulty in swallowing	10	130	+
969	F	2	Rigidity of neck, double Kernig. Tremulous, right knee-jerk exaggerated, left very weak, weakness of right side of face, left leg and internal recti	8	17	+
970	M	1 5/12	Retraction of head, Marked weakness of muscles of neck, right side of face and tongue. Knee-jerks absent	10	104	+
974	F	8	Weakness of muscles of right side of face. Knee-jerks exaggerated. Rigidity of neck. Marked colitis	10	44	+
977	F	2	Knee-jerks unequal. Weakness of right foot, right eyelid, and right side of face	10	83	+
981	F	8/12	Retraction of head. Tremors. Knee-jerks exaggerated. Weakness in extensors of hands	2	475	+++
982	M	3	Retraction of head. Weakness of muscles of right side of face. Inequality of knee-jerks	12	25	+
986	F	5/12	Rigidity of neck. Double Kernig. Doubtful weakness of right arm	..	..	..
994	F	4	Comatose. Severe twitching of muscles. Rigidity of neck. Double Kernig and Babinski. Knee-jerks exaggerated. Partial paralysis right side of the face	10	19	+
1000	M	3	Almost complete paralysis left side of face. Marked weakness of muscles of neck. Strabismus. Marked ataxia	5	955	++

almost normally when brought to a sitting position, and he walked without ataxia. There was no apparent weakness of the arms or legs. He could close his left eye completely. Eight c.c. of serum were given.

*Oct. 15.*—Complete recovery except slight weakness of the left side of the face, noticeable only on crying and laughing. Rapidly improving.

## RESULTS

**GROUP 2.**—*Patients showing slight paralysis at the time of the serum treatment.* In 16 of the 17 patients in this group the paralysis was arrested, the fever and symptoms disappeared promptly, and the restoration of function of the paralyzed or weakened muscles occurred rapidly, particularly in Cases 947, 951, and 994. The 16 patients were well,

## PARALYSIS AT THE TIME OF SERUM TREATMENT

DAY OF DISEASE	TEMPERATURE AT TIME OF TREATMENT	TOTAL AMOUNT OF SERUM GIVEN, C.C.	RESULT
4	101	7.5	Temperature dropped promptly, mental condition improved, weakness of face disappeared entirely
1	104	11	Temperature dropped abruptly. Prompt and complete recovery
2	101.5	10	Prompt disappearance of temperature. No extension of paralysis. Rapid and complete recovery
2	99.8	22	Headache and muscular twitchings disappeared during serum injection. Ability to swallow returned within one hour. Complete recovery in twenty-four hours
1	99.6	32	Prompt and complete recovery. No extension of paralysis
1	103	6	No extension of paralysis. Temperature dropped by crisis. Complete recovery
2	101.4	23.5	Distinct extension of paralysis of right leg. Ultimate complete recovery
3	102	5	Temperature disappeared promptly. No extension of paralysis. Complete recovery
4	102	15	No extension of paralysis. Rapid and complete recovery
4	100.6	10	No extension of paralysis. Marked early improvement. Complete recovery
2	98.6	10	No extension of paralysis. Complete recovery
2	100.4	6	No extension of paralysis. Complete recovery
3	102.8	12	No extension of paralysis. Complete recovery
2	102	9	Rapid disappearance of temperature. No extension of paralysis. Complete recovery
1	102.2	5	Prompt recovery
1	104	17.5	No extension of paralysis. Complete recovery within twenty-four hours
4	101	18	Prompt improvement following both serum injections. Almost complete recovery. Slight weakness of left side of face

with complete restoration of muscle-function in from one to seven days after the serum was given. One patient (Case 958) who had severe infection of the tonsils with enlarged paratonsillar glands showed a slight extension of weakness in the right thigh, but six weeks later restoration of muscle-function was nearly complete. The age of the patients in this group ranged from five months to twenty-three years, the average being five years (Table 2). Eight were males and 9 were females. The spinal fluid was under increased pressure in all the cases in which the puncture was successful. In one (Case 986) the dura was not punctured. In three the fluid was distinctly turbid, and in the others it was clear. The amount withdrawn ranged from 0.3 c.c. to 35 c.c., the average being 12 c.c. The cell count ranged from 9 to 955

cells per cubic millimeter, the average count being 149. The globulin test was positive in all. The temperature at the time of the first injection was between 98 and 102 in 12 of the cases, between 102 and 103 in 3, and 104 in 2. The pulse was unusually rapid, as in the patients in Group 1.

The serum treatment was begun on the first day in 5 cases, on the second day in 6, on the third day in 2, and on the fourth day in 4. In 10 cases only one injection was given, in 6 two injections, and in 1 three injections. The amount given ranged from 5 to 32 c.c., the average being 13 c.c. A prompt drop in temperature and pulse-rate occurred in nearly all instances. The improvement in this group was quite as striking as that in Group 1, and could be measured more accurately by noting the improvement in the function of the weakened or paralyzed muscles. The drop in the temperature and pulse-rate in this group, as in Group 1, occurred without an initial rise (Chart 2). The symptoms in some patients, as of those in Group 1, began to disappear while the serum was being slowly injected, or soon thereafter (Cases 947, 951, 994, and 1000), and in at least one patient (Case 994) unmistakable symptoms of a rapidly progressing bulbar type of the disease disappeared promptly after the injection of serum, recovery being practically complete within twenty-four hours.

#### CASES SHOWING ADVANCED PARALYSIS AT THE TIME OF SERUM TREATMENT

CASE 931.—H. M., a boy, aged six years. (Patient of Dr. D. G. Kreul, Davenport, Iowa.)

*Aug. 29.*—The patient was perfectly well until eight days before, when for several days he had a slight fever and did not eat well. He then appeared well until five days later, when he complained of pain in the back of the neck and of feeling sick all over. He felt hot and vomited, was restless, tossed about, and talked continuously in his sleep. There was pain and stiffness of the neck. The pain in the neck was aggravated on attempting to flex the head. The pulse was rapid and the temperature 100.5. The following day his condition was much the same but the temperature was 101.5. There was no evident paralysis. On the morning when first seen the pain and stiffness in the neck had disappeared. He awakened his father at 5 o'clock telling him that he could not move his right arm; his temperature was 101.6. *10 P. M.*—There was almost complete flaccid paralysis of the right shoulder, extension of the right hand was weak, the grasping power quite well preserved. There was definite weakness in the right leg, but he could

kick a hand with the leg held in extended position. The knee-jerk on the right side was absent, on the left diminished. There was tremor of the muscles of the jaw and complaint of pain in the right ankle.

*Aug. 30, 2 P. M.*—Pain in the right ankle and leg was still present. The patient was restless and the paralysis had extended. Knee-jerks on both sides were absent and the child was unable to lift the right leg in extended position. The left eyelid drooped, there was tremor of the muscles of the jaw and lips, and marked weakness of the muscles of the neck. The temperature was 101.8, the pulse 140. A spinal puncture was made, the fluid was under pressure, and 15 c.c. were withdrawn. Cell count, 135, globulin test +. Four c.c. of immune serum were injected intravenously. No untoward symptoms followed the injection. *9 P. M.*—The child rested and slept quietly for two hours after the injection of serum, for the first time since the onset of the illness. The pain in the right leg had disappeared. Eight c.c. of serum were injected.

*Aug. 31, 8.30 A. M.*—The parents stated that the boy slept quietly without awakening until 4 A. M. He looked bright and appeared rested. The tremor of the muscles of the jaw and the drooping of the left eyelid had disappeared. There was no extension of paralysis in the right shoulder and he could again lift the right leg in extended position. The temperature was normal. *8.30 P. M.*—Undoubted improvement had occurred in the right arm. He could reach for things on the opposite side of his body. He kicked a hand  $1\frac{1}{2}$  feet above the bed with the right leg in extended position. The knee-jerk on the left side had returned. Eight c.c. of serum were injected.

*Sept. 2.*—There was marked improvement in muscle power in the right arm and leg, and the muscles of the neck were stronger. He appeared well.

*Sept. 27.*—The boy was up and around and walked without dragging the right foot. There was still slight weakness in the muscles of the back. He was able to move the right arm in every direction, but could not yet hold the arm in a horizontal position.

*Oct. 15.*—There was almost complete restoration of muscle function. (Temperature and pulse curves, Chart 3.)

**CASE 932.**—W. D., a boy, aged three and three-fourth years. (Patient of Dr. W. Matthey, Davenport, Iowa.)

*Aug. 30.*—There had been fever, vomiting, and diarrhea four days before. The child became very tremulous and nervous and this condition was soon followed by drowsiness and listlessness. A slight weakness of the left leg was noted three days later. The boy dragged the left foot, was cross, and complained of pain in the left leg. *3 P. M.*—There was evident weakness in both legs, but more marked in the left; he was unable to walk, but could still lift the left leg in extended position. The knee-jerk was absent on the left side and barely obtainable on the right. There was rigidity of the neck and attempts at flexion caused

pain. 5 P. M.—The weakness in the legs had increased markedly. He was now entirely unable to lift the left leg from the bed or to flex the thigh. The temperature was 101.5, the pulse very rapid. A spinal puncture was made. The fluid was under pressure and 12 c.c. were obtained. Cell count 94, globulin test +. Four c.c. of serum were given; no untoward symptoms followed the injection.

Aug. 31, 1 P. M.—The general condition had improved. He was no longer drowsy or listless, but appeared bright and had slept better than on previous nights. The paralysis had not extended. The knee-jerk on the left side was still absent, while that on the right was more vigor-

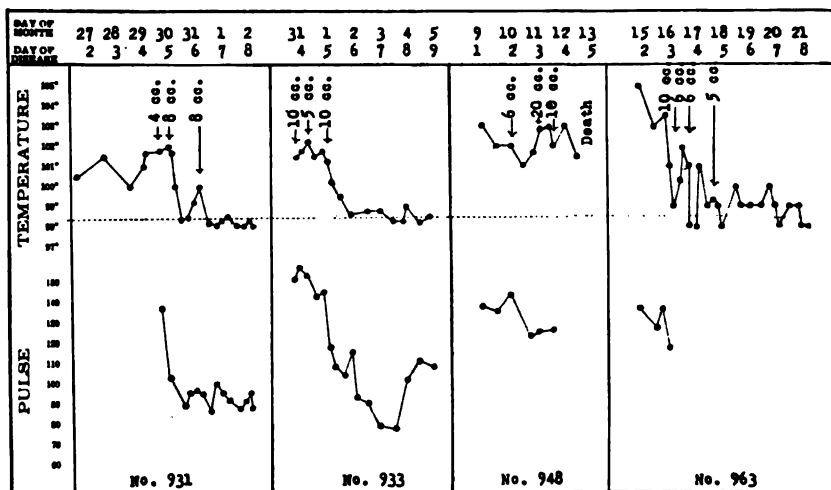


Chart 3.—Temperature and pulse curves of patients showing advanced paralysis at the time of serum treatment.

ous. The temperature was normal. Seven and one-half c.c. of serum were given.

Sept. 1, 12 M.—A spinal puncture was made, the fluid was not under pressure, and 1 c.c. of clear fluid was obtained. The general condition was good. There was undoubted increase in strength in both legs. He complained of pain in the left leg. Six c.c. of serum were given. Improvement in muscle-function was rapid. The pain and the tendency to draw up the leg continued for some time. Three weeks later the boy could ride a tricycle, but was not yet quite able to bear his weight on the left leg.

CASE 933.—L. C., a girl, aged eight years. (Patient of Dr. P. A. Bendixon and Dr. Wm. H. Rendleman, Davenport, Iowa.)

Aug. 31.—The tonsils and adenoids were removed three years previously and there had been no trouble with the throat since that time.

The girl had an attack of indigestion one month previously, but recovered completely following the administration of laxatives. She had remained well until a week before, since which time she had felt ill. Four days before she complained of having pain and a lump in her throat. Three days before she began to vomit, had fever, a temperature of from 101 to 102, and the vomiting continued. She was unable to keep anything on her stomach. There was retraction of the head and pain in the neck and throat; she was extremely restless, nervous, irritable, and trembly at times. The day before she began to have trouble in swallowing and choked at every attempt to swallow.

*Aug. 31, 2 P. M.*—She had repeated choking spells in which she became cyanotic and death appeared imminent. She was unable to speak, her face was much distorted, she was utterly unable to swallow, and there were almost constant attempts at vomiting. The muscles of the pharynx and the tongue were very weak, the throat was diffusely hyperemic and thickly covered with mucus. There was a moderate amount of infected lymphoid tissue in the region of the left tonsil. The thyroid was enlarged. There was marked weakness of the muscles of the neck and tremor of the muscles of the forearm. The pupils were dilated. There was marked pallor. The temperature was 101.4, the pulse 160, and the respiration shallow. The expansion of the chest was diminished in its upper portion; the respirations were chiefly diaphragmatic and there was moderate cyanosis. A spinal puncture was made, the fluid was under marked pressure, and 30 c.c. were withdrawn. Cell count 165, globulin test ++. Ten c.c. of serum were given. *9.30 P. M.*—The girl had rested quietly most of the time since the injection of the serum. She had slept at intervals, the pulse was less rapid and of better quality. She could swallow better and the cyanosis was absent. Five c.c. of serum were given.

*Sept. 1, 10 P. M.*—There was a marked change in the condition of the patient. Cyanosis had disappeared. Expansion of the chest was normal. She could speak. The weakness of the muscles of the neck was less marked, but there was still difficulty in swallowing. Vomiting had entirely disappeared. Fluids and nutrients were given per rectum. Ten c.c. of serum were given.

*Sept. 2.*—The temperature was normal, and there was marked change for the better in every respect. She could swallow small amounts of liquid with the head held to the left side. There was pain in the back of the neck. *9.30 P. M.*—The pain in the back of the neck had disappeared, but there was some difficulty in swallowing for a week. There was general improvement from the time of the first injection of serum. Five weeks later there was no evidence of paralysis anywhere except a slightly drawn condition of one side of the face, and no difficulty in swallowing meat. The girl was perfectly well.

(Temperature and pulse curves, Chart 3.)



CASE 934.—A. H., a boy, aged two years. (Patient of Dr. L. F. Newburn, McCausland, Iowa, and Dr. J. T. Haller, Davenport, Iowa.)

*Aug. 31.*—The patient was perfectly well until three days before, when he became drowsy and prostrated; he vomited, had diarrhea and was feverish. There was retraction of the head. The temperature was 102. There was paralysis on the right side of the face two days later, but no other weakness was noted. *2 P. M.*—There was marked weakness of the muscles of the neck; he was unable to hold his head erect. The right side of the face was completely paralyzed, he could not close the right eye, and the paralysis was rapidly extending. The temperature was normal, the throat and tonsils reddened, and a large amount of pus was expressed from the pole of the left tonsil, but none from the right. An enlarged lymph-gland was noted outside the tonsil on the left side, but none on the right. The knee-jerks were normal. A spinal puncture was made, the fluid was under pressure, and 15 c.c. were withdrawn. Cell count 60, globulin test +. Six c.c. of serum were given.

*Sept. 1.*—The temperature was normal. The child appeared brighter. There was no extension of paralysis.

*Sept. 12.*—There was complete recovery except slight weakness of the right eyelid.

This patient was in the country. A neighbor's child had recently died of "intestinal disturbance," with pain and rigidity of the neck. There had been no contact until three days before the onset of the symptoms in this child.

CASE 935.—C. S., a girl, aged eighteen months. (Patient of Dr. D. G. Kreul, Davenport, Iowa.)

*Aug. 31.*—Typical onset two weeks previously with restlessness, vomiting, fever, hyperesthesia, pain in the back of the neck, retraction of the head, followed by almost complete paralysis of the lower extremities. Restlessness was still present, although the temperature had been normal for ten days. The patient continued to have crying spells for an hour at a time and there was no improvement in the paralysis. Because of this it was thought that the serum might still do some good. *9 P. M.*—A spinal puncture was made, the fluid was under slight pressure, and 15 c.c. were withdrawn. Cell count and globulin test negative. Five c.c. of serum were given.

*Sept. 1.*—There was no apparent change except that the baby rested better. The crying spells and the restlessness had disappeared.

*Oct. 15.*—Only moderate improvement in muscle-function; marked weakness in legs.

CASE 937.—L. B., a boy, aged four years. (Patient of Dr. F. Neufeld, Davenport, Iowa.)

*Sept. 1, 2 P. M.*—There had been vomiting, diarrhea, headache, retraction of the head, marked tremor, and high fever since the day before. On our arrival the patient was dying from respiratory failure.

He was gasping for breath, there was marked cyanosis, the pulse was barely obtainable, and the extremities were cold. The thorax was immobile and there was very faint contraction of the diaphragm. He was kept alive by artificial respiration for a number of hours. A spinal puncture was made, the fluid was under pressure, and 10 c.c. were obtained. Cell count 185, globulin test ++++. Two and one-half c.c. of serum were injected intraspinaly and 16 c.c. intravenously. There was no apparent effect and the cyanosis continued despite the artificial respiration. The patient died two hours later.

CASE 938.—H. K., a boy, aged twelve years. (Patient of Dr. F. E. Rudolf and Dr. L. F. Guldner, Davenport, Iowa.)

*Sept. 3.*—The child was apparently well until three days before, when he felt sick, acted strangely, and was extremely restless. He vomited nearly all of the following night. The next day he had severe pain in the back of the head and neck; the neck was stiff; the temperature was 101. He was tender everywhere, did not want to be handled, and was extremely restless. Trouble in swallowing began that night. The temperature was 105. The difficulty in swallowing grew steadily worse during the day. He developed great weakness of the muscles of the arms, the neck, and the face. *4.30 P. M.*—The throat was hyperemic, the tonsils large and infected. One large cervical gland was noted just outside each tonsil and a second gland outside the right. There was complete paralysis of the arms, the muscles of the neck, and thorax, and the respirations were entirely diaphragmatic. The child choked with every attempt to swallow. There was a mucous rattle in the throat and frothy mucus flowed from the mouth. The extremities were cold; there was clammy sweat on the face; the eyes turned back; there was marked cyanosis; the skin was dusky and mottled; the radial pulse was barely perceptible. The patient continued to be extremely restless and tossed about incessantly in attempting to swallow and to get his breath. A spinal puncture was made, the fluid was under marked pressure, and 20 c.c. were obtained. Cell count 320, globulin test ++++. The patient had had diphtheria antitoxin some years previously. Twenty-five one-hundredths c.c. of serum was given intravenously, followed in thirty minutes by 5 c.c., and in two hours by 12 c.c. *7 P. M.*—The extremities were warm, the pulse was easily perceptible and regular but rapid. The chest was immobile. *8.30 P. M.*—Died.

CASE 942.—C. E., a boy, aged eleven months. (Patient of Dr. R. Dart, Rock Island, Illinois.)

*Sept. 6.*—The infant was perfectly well until eight days previously, when he had fever which was thought to be due to teething, three teeth being in the process of eruption. He had been feverish ever since. The temperature five days before was 102.5, four days before, 100. During most of this time there was constipation, but the last two days there was slight diarrhea with green stools. A peculiar staring condi-

tion developed the day before. The head was retracted, the eyes were rolled back, and he was unable to nurse. Severe convulsions in the morning were followed by difficulty in swallowing. The temperature was 101. 1 P. M.—The left arm and leg were held stiff; the fingers of the right hand were flexed tightly. There was a peculiar staring condition of the eyes. The child was semicomatose; the head retracted and the neck stiff. The temperature was 100, the pulse 110. The tonsils were large; a large amount of pus was expressed from the left. Two enlarged lymph-glands were palpable on the left side of the neck, just outside the tonsils, but none on the right. The head and neck were held stiff. There was bulging of the fontanels. He was unable to close the left eye. The left side of the face was partially paralyzed. The knee-jerks were exaggerated. He was unable to extend the left index-finger and the thumb. The bowels were flushed with a hypertonic solution of sodium chlorid and sodium bicarbonate. A large amount of fecal material containing a moderate amount of mucus was obtained. A spinal puncture was made, the fluid was under pressure, and 12 c.c. were withdrawn. Cell count 144, globulin test +. The spastic condition of the left arm and leg was not relieved for an hour after the spinal puncture and there was a generalized spasm with retraction of the head fifteen minutes afterward. The temperature was 100, the pulse 130. 2 P. M.—Five c.c. of serum were given. Ten minutes after injection of the serum the staring disappeared from the eyes, the left arm and leg relaxed, the baby yawned normally, and went to sleep with the eyes completely closed for the first time in twenty-four hours.

*Sept. 7, 9 A. M.*—The child rested quietly all the afternoon and evening. The left arm and leg were relaxed. During the night the baby had spells when the arms and legs were set; one severe spasm occurred at midnight and 7 or 8 lighter spasms after that time. The child lay quietly with the eyes open; there was less rigidity of the neck. The fontanels bulged and pulsated with each pulse-beat. A spinal puncture was made, the fluid spurted, and 15 c.c. were withdrawn. Cell count 80, globulin test +. Ten c.c. of serum were given. There was no apparent increase in the paralysis.

*Sept. 9, 1 P. M.*—The condition was about the same. There was no apparent increase in the paralysis, but there was general spasticity of the legs and arms, and the neck was rigid. The child was semicomatose. Ten c.c. of serum were given. The spastic condition of the arms and legs largely disappeared thirty minutes after the injection of the serum. He moved both legs. 9 P. M.—The condition of the patient was better. The temperature was normal. The spastic condition of the arms and legs had disappeared. He was able to swallow barley water. There were no spasms since the serum was given in the afternoon.

*Sept. 10, 2.30 P. M.*—The arms and legs were relaxed. There was no retraction of the head. The mouth closed. There was marked exhaustion, the extremities were cold, there was a mottling of the skin

and cyanosis; the pulse was 180. 6.30 P. M.—Death occurred, apparently from exhaustion.

CASE 943.—E. S., a boy, aged two years. (Patient of Dr. E. P. Ficke, Davenport, Iowa.)

Sept. 7.—The child was slightly indisposed incident to the eruption of a tooth two weeks previously. He did not appear to have fever and was well until 10 A. M. the day before. Since then he had whined and felt generally miserable. He was restless and hot all night; vomited his supper at 7 in the morning and at 9 A. M. he vomited a large amount of slimy material streaked with blood. He insisted on being held and was very drowsy all the forenoon. 12.15 P. M.—The temperature was 102.3, the pulse 150. The respirations were jerky. The right knee-jerk was normal, the left sluggish. He was tremulous and ataxic, scarcely able to walk, and tended to fall to the left. There was marked distention of the abdomen. 5 P. M.—He was very drowsy, could scarcely be aroused; he lay with head retracted, eyes rolled back, mouth open. He was unable to walk, was very ataxic and tremulous, falling to the left, and there was marked weakness of the left leg. The temperature was 103, the pulse 130 and irregular. There was alternate flushing and pallor of the skin. There was paralysis of the left side of the face and he was unable to close the left eye. The arms and legs were tremulous; the knee-jerk on the right side was markedly exaggerated, that on the left side was not obtainable. The breathing was jerky. There was no expansion of the upper part of the chest. The respirations were almost wholly diaphragmatic. There was moderate cyanosis. A large amount of mucopurulent material was found in the nasopharynx. The throat was moderately reddened and the tonsils were large. A small amount of pus was expressed from the pole of the left tonsil. 5.30 P. M.—A spinal puncture was made, the fluid spurted, and 15 c.c. were obtained. Cell count 120, globulin test +. Ten c.c. of serum were given. 8 P. M.—The temperature was 102.2. The bowel movements contained a large amount of mucus. 10.30 P. M.—The temperature was 103. The general condition was about the same. There was marked trembling in the arms.

Sept. 8, 4 A. M.—The parents became greatly alarmed; the child jumped up into sitting position, apparently strangling in an unsuccessful attempt to vomit, and turned white and cold. The bowels moved during this attack and again in twenty minutes, the movements containing a large amount of mucus. The temperature was 103. There was vertical nystagmus. The expansion of the upper chest had returned and the paralysis had apparently not extended. There was less retraction of the head. The child appeared more relaxed and there was less trembling.

Sept. 8, 5.30 A. M.—Six c.c. of serum were given. 11 A. M.—The temperature was 105. There was marked cyanosis and rattling in the

throat. 11.30 A. M.—Death occurred from edema of the lungs and respiratory failure.

CASE 945.—V. S., a girl, aged fourteen years. (Patient of Dr. L. F. Sullivan, Donahue, Iowa, and Dr. F. Lamback, Davenport, Iowa.)

Sept. 8.—The patient had had an enlarged thyroid for two years. About three weeks previously an abscessed tooth had caused toothache. A dentist had treated it three times and filled it five days previously. For a number of days there had been pain in the side of the face and about the ears which was thought to be due to the teeth. Pain in the epigastrium four days previously had been relieved with castor oil. She had high fever four nights before and was generally ill. The morning before, while drying dishes, her legs suddenly became weak and she fell in walking up a few steps, but was able to walk to bed with her mother's help. 2 P. M.—The knee-jerks were absent. There was no apparent weakness in the arms. 6.30 P. M.—She appeared quite well while lying in bed, and did not complain of pain. The thyroid was large and firm. There was slight stiffness of the neck, and attempt to flex the head caused pain. There was absence of knee-jerks on both sides; marked Kernig and almost flaccid paralysis of legs and arms. When the arms and legs were lifted from the bed, they dropped limply. On examining the tonsils the muscles of the jaw and lips were very tremulous. There was marked photophobia, both vertical and horizontal nystagmus, and marked drooping of the eyelids. There was much phlegm in the throat, the tonsils were large, and pus was expressed from the pole of the right. There were two small glands outside the right tonsil and one on the left. A spinal puncture was made, the fluid was under moderate pressure, and 15 c.c. were obtained. Cell count 130, globulin test +. Five-tenths c.c. of serum was given intravenously, followed in one hour by 12 c.c. intravenously. The patient had had diphtheria antitoxin some years previously.

Sept. 9, 5 P. M.—There was no demonstrable increase in the paralysis anywhere and undoubted improvement in the extensors and flexors of the forearms. Twelve c.c. of serum were given.

Sept. 10.—No apparent extension of paralysis.

Sept. 11.—Photophobia was absent. The nystagmus had disappeared. She could rotate the legs and open the eyes normally.

Sept. 15.—There was severe urticaria associated with pain in the extremities and spasms of the muscles of the back.

Sept. 29.—The patient was able to sit up in a wheel-chair. She could bring both hands to her mouth. There was no paralysis of eyes or face. The grasping power in the arms was quite marked. She had some strength in the lower extremities, but was still unable to walk. The knee-jerks were absent.

Oct. 16.—There was marked improvement in muscle power, especially of arms, perfect control, except of right deltoid. The power in the lower extremities was gradually returning.

CASE 948.—B. W., a girl, aged eleven years. (Patient of Dr. F. Neufeld, Davenport, Iowa.)

*Sept. 10, 8 A. M.*—The patient was well until the morning before, when she awoke with headache and pain in the back of the neck. She did not eat breakfast or dinner. The temperature was 102, the pulse 138. There was tremor of the hands, and the neck was stiff. *2 P. M.*—She vomited. The temperature was 103, the pulse 140. *6 P. M.*—The temperature was 102, the pulse 145. *9 P. M.*—The face was flushed, the head retracted. There was marked photophobia, the eyes were partially closed. The throat was hyperemic, containing a large amount of mucus. The tonsils were enlarged, especially the left, and a large amount of pus was expressed from the pole. There was an enlarged lymph-gland outside the left tonsil; none on the right side. While examining the throat the muscles of the face were very tremulous. She was ataxic. The neck was stiff and painful and the right side of the face and the eyelids were partially paralyzed. The knee-jerk was active on the right side, but hard to obtain on the left side. Kernig was present on both sides. The temperature was 102, the pulse 145. She was apathetic and drowsy, could be aroused, but immediately went back to sleep. A spinal puncture was made: the fluid was under moderate pressure and distinctly turbid; 20 c.c. were obtained. Cell count 316, globulin test ++. Six c.c. of serum were given.

*Sept. 11, 9 A. M.*—She looked brighter. Photophobia was present. The paralysis of the right side of the face was marked. She complained of headache. There was less rigidity of the neck. She was ataxic. Slight weakness was noticeable in the legs when she walked. The temperature was 101 at 2.50 in the morning. White blood count 13,200. *1 P. M.*—She had been drowsy most of the forenoon, and still complained of pain in the neck and back. She appeared very sick. There was undoubted extension of the paralysis; photophobia was marked. There was lateral nystagmus of both eyes; she was unable to raise the eyelids completely. The temperature was 101.6, the pulse 124. The right arm was weak, and the grasping power of the hands was diminished on both sides. The expansion of the upper chest was limited. Twenty c.c. of serum were given. Soon after the injection the patient appeared brighter, took interest in her surroundings, and said that the headache had disappeared. *6 P. M.*—The temperature was 103, the pulse 128. The general condition was about the same. There was no apparent extension of the paralysis.

*Sept. 12, 8.45 A. M.*—The temperature was 103, the condition worse. There was only slight expansion of the lower portion of the chest; the upper portion was immobile and respirations were almost wholly diaphragmatic. She was cyanotic and seemed anxious and air hungry. Her voice was weak and tremulous. *10 A. M.*—The temperature was 102, the pulse 128. The condition was rapidly growing worse. She was comatose and there was marked weakness of both arms. The knee-

jerks were absent, the plantar reflexes were weak and much delayed. She was unable to lift her legs from the bed in extended position, but could flex them at the knees. Extension and flexion of feet were normal. Respirations were diaphragmatic. The abdomen was tympanitic and there was tenderness in the upper half. A spinal puncture was made, the fluid was clear and under slight pressure; 10 c.c. were obtained. Ten c.c. of serum were given.

*Sept. 13.*—The patient died at 2.50 A. M.

(Temperature and pulse curves, Chart 3.)

CASE 949.—S. C., a girl, aged seventeen years. (Patient of Dr. L. F. Newburn, McCausland, Iowa.)

*Sept. 11.*—The patient was perfectly well until four days before, when she had a headache thought to be due to a bilious attack, since she had been subject to such attacks. The following day she vomited repeatedly, she was restless, nervous, and was unable to sleep that night. The next day she felt no better and noticed a peculiar twitching of the muscles. She sat at the table at noon and then went to bed. Several hours later she got out of bed and in attempting to walk fell to the floor and had to be lifted into bed because of weakness of the legs. 6 P. M.—There was almost complete flaccid paralysis of the legs and marked weakness of the arms. Air-hunger and partial paralysis of the muscles of the chest were noted. The temperature was 100.

*Sept. 12, 1.30 A. M.*—The patellar, triceps, and biceps reflexes were absent. The head was retracted, the voice was very weak and tremulous, and the respirations labored; there were symptoms of air-hunger. The diaphragm was immobile and the excursions of the thorax were limited. She had difficulty in swallowing. There was almost complete flaccid paralysis of the upper and lower extremities; she could just bring the left hand to her mouth. There were marked tremor and twitching of the muscles about the face. The temperature was 101. The throat was hyperemic, the left tonsil was large, the right small. A moderate amount of pus was expressed from the pole of the left tonsil, none from the right. There was a large amount of thick, glairy, mucopurulent material in the nasopharynx. There were two enlarged lymph-glands on the left side of the neck, just outside the tonsil, none on the right side. The thyroid was enlarged. A spinal puncture was made: the fluid was under moderate pressure, was slightly bloody and turbid, and 20 c.c. were obtained. Ten c.c. of unactivated serum were injected intraspinally and 25 c.c. intravenously. 6.30 P. M.—She was comatose, the head was retracted, and she was markedly cyanotic. There was a mucous rattle in the throat. The excursion of the thorax was slight, the diaphragm immobile. There was a relaxation of the abdominal walls. 7 P. M.—The patient died.

CASE 955.—W. N., a boy, aged thirteen months. (Patient of Dr. H. U. Braunlich, Davenport, Iowa.)

*Sept. 13.*—The child had been perfectly well until 2 A. M. three days before, when he vomited, had high fever, and was cross and fretful. The fever continued for three days and the condition was thought to be la grippe, since other members of the family had had similar attacks. The afternoon before he had been unable to sit up and constantly fell forward. There was marked weakness of the muscles of the neck and the legs. 9 P. M.—The temperature was 99.8. There was flaccid paralysis of the lower extremities and marked weakness of the muscles of the back, the neck, and the left arm. He was fretful and irritable, and when handled appeared to be in pain. The tonsils were rather large. There was a large lymph-gland on the left side of the neck outside the tonsil, none on the right side. A spinal puncture was made, the fluid was under pressure, and 20 c.c. were obtained. Cell count 133, globulin test ++. Six c.c. of serum were given.

*Sept. 14.*—The temperature was normal and there was less restlessness and no extension of paralysis, otherwise but little change.

*Oct. 15.*—Marked improvement. The child was able to stand erect.

CASE 957.—L. S., a girl, aged nine months. (Patient of Dr. S. G. Hands, Davenport, Iowa.)

*Sept. 14.*—The child became ill five days before with fever and vomiting. The temperature the second day was 99.2. She appeared drowsy and slept most of the time with head retracted and eyes partly open. The left leg was weak for two days. 10.30 A. M.—The left leg was almost completely paralyzed. The right eye was turned in and there was marked weakness of the muscles of the neck and back and she was unable to hold up her head or sit up. The tonsils were large. The throat was diffusely hyperemic, with profuse secretion in the pharynx. There was one lymph-gland on either side just outside the tonsil. A spinal puncture was made, the fluid was under pressure, and 10 c.c. were obtained. Cell count 30, globulin test ++. Six c.c. of serum were given.

*Sept. 15.*—There was no extension of paralysis.

*Oct. 15.*—Marked improvement was noted soon after administration of the serum.

CASE 959.—D. C., a girl, aged twelve months. (Patient of Dr. C. C. Sloan, Moline, Illinois.)

*Sept. 14.*—The child was taken sick four days previously with high fever, vomiting, and diarrhea. The abdomen was distended, the stools green and of foul odor. There was marked depression and a tendency to sleep constantly with the head retracted. Paralysis of the lower extremities appeared the day before, and difficulty in swallowing began in the morning. 4 P. M.—There was complete flaccid paralysis of the lower extremities; the knee-jerks were absent. She was comatose and cyanotic, there was a mucous rattle in the throat, and she was unable to swallow. The upper portion of the chest was paralyzed. She was restless and the eyeballs and muscles of the hands twitched. The ex-



tremities were cold. There were retraction and rigidity of the neck. The temperature was 104; the pulse was not obtainable. A spinal puncture was made, the fluid was under pressure, and 10 c.c. were withdrawn. Cell count 58, globulin test ++. Six c.c. of serum were given. 5 P. M.—The restlessness had disappeared; she had fallen asleep with eyelids closed. The twitching of the hands had disappeared. 10 P. M.—The patient died of respiratory failure.

CASE 960.—E. S., a girl, aged sixteen years. (Patient of Dr. C. F. Cron, Long Grove, Iowa.)

Sept. 15.—The patient had had severe headache, fever, and dizziness with repeated vomiting the afternoon before, in the night and almost constantly during the next forenoon. There was marked weakness of the legs, paralysis of the left side of the face, and external strabismus of the left eye. Inability to swallow began in the night. 9 A. M.—The voice was husky and tremulous. The patient tossed about in attempts to swallow. She vomited a large amount (fully two quarts) of mucus containing discolored blood, at frequent intervals. There were cyanosis, intense thirst, air-hunger, and she was entirely unable to swallow. The eyes turned sharply inward, the head was retracted, and the neck stiff. Kernig +. The knee-jerk on the left side was normal, but absent on the right side. There was a large amount of secretion in the pharynx. The tonsils were of moderate size; a palpable lymph-gland was noted on either side. Marked Babinski. There was complete paralysis of the left side of the face. She was unable to open her mouth more than 1.5 cm. There was marked weakness of the extensors of the left arm. Expansion of the chest was limited. The temperature was 103. A spinal puncture was made, the fluid was under increased pressure and distinctly turbid, and 15 c.c. were obtained. Cell count 344, globulin test ++++. Twelve and one-half c.c. of serum were given. The patient was quieter for several hours after the injection then became restless again and died six hours later of respiratory failure.

CASE 963.—M. S., a boy, aged three years. (Patient of Dr. D. G. Kreul, Davenport, Iowa.)

Sept. 16.—The child was restless and irritable and unable to sleep four nights before. The next day he complained of pain in the throat, he was irritable and feverish in the morning, with high fever at night. The following night he vomited three times, and was restless and unusually drowsy. The next day there was marked jerking of the muscles, and weakness of the muscles of the neck and arms developed during the night. 11.50 A. M.—The child was extremely ill. His face was alternately flushed and pale, and he lay with head retracted and eyes turned in sharply. There was marked twitching of the eyeballs. He cried out at frequent intervals and threw himself from side to side. Attempts to flex the head caused pain. Kernig marked. He was tremulous and unable to stand because of weakness of the legs. The

right knee-jerk was obtainable, the left absent. He could not hold up his head. He had great difficulty in swallowing and there was a mucous rattle in the throat. The muscles of the chest apparently were not affected. Both arms were very weak and he was unable to bring his hands to his mouth. There were coarse râles over the chest. He was semicomatose. The temperature was 103.5. A spinal puncture was made, the fluid was under increased pressure, clear, and 3 c.c. were withdrawn. Cell count 277, globulin test + + +. Ten c.c. of serum were given. 12.22 P. M.—The child was quieter. Nystagmus and strabismus were less marked. 8.30 P. M.—The child appeared brighter and was undoubtedly better. The twitching of eyeballs and the strabismus were gone. The color was good. He could swallow without difficulty. Respirations were normal, the head less retracted, the face symmetric. The muscles of the neck were undoubtedly stronger, but there was no change in the weakness of the arm. Six c.c. of serum were given.

Sept. 17, 12 M.—He slept quietly. The retraction of the head was less marked and the alternate flushings and pallor had disappeared. The pupils were equal. There was no strabismus. Excursions of the chest were normal. He was interested in the surroundings. The left knee-jerk was barely obtainable, the right slightly plus. Kernig less marked. The muscles of the neck were stronger, the arms were weak. There was no extension of the paralysis. Six c.c. of the serum were given.

Sept. 18, 12 M.—The child slept well the night before. His color was good. He was able to hold his head erect when in a sitting position. He had no difficulty in swallowing and could bring his left hand to his mouth. The knee-jerk on the right side was normal, on the left side diminished but obtainable. Five c.c. of serum were given.

Sept. 20.—The child was much brighter. The right eye tended to turn inward at intervals, the face was symmetric, there was no difficulty in swallowing, the head was held erect when in sitting position. He could move his arms in every direction but there was slight weakness. The knee-jerks were normal.

Oct. 15.—There was marked improvement in muscle-function.

Nov. 8.—Complete recovery assured.

(Temperature and pulse curves, Chart 3.)

CASE 967.—L. B., a girl, aged seven years. (Patient of Dr. M. S. Jordan, Clinton, Iowa.)

Sept. 17.—Two weeks before the child became ill with vomiting, projectile in character, high fever, and severe headache. She was extremely restless and tremulous. She was mentally apathetic, drowsy, and then semicomatose, with retraction of the head. The extremities were spastic. 11.45 P. M.—The temperature ranged from 99 to 103. She lay in bed, comatose, with the head retracted, and could not be

aroused. Tache cérébrale was marked. Knee-jerks were absent. Marked Kernig and Babinski signs. The muscle tonus of the arms was increased. There was almost complete flaccid paralysis of the right leg, and combined flaccid and spastic paralysis of the left. The tonsils were normal in size, and there were enlarged cervical glands outside of both tonsils. There was much mucus in the pharynx. A spinal puncture was made, the pressure was not increased, and 10 c.c. of clear fluid was obtained. Cell count 50, globulin test + +.

*Sept. 18, P. M.*—The patient was comatose and weaker. Ten c.c. of unactivated serum were given.

*Sept. 19.*—The patient died.

CASE 978.—F. E., a girl, aged three and one-half years. (Patient of Dr. P. H. Wessel, Moline, Illinois.)

*Sept. 24.*—Four days previously the child had had headache, pain in the back of the neck, twitchings of the muscles, and high fever. The temperature was 103.5, the pulse rapid. The fever continued high for three days. Weakness of left leg was noted two days before, more marked the following day. *4.30 P. M.*—There was almost complete flaccid paralysis of the right arm and left leg and the muscles of the neck were weak. The tonsils were diffusely red, and pus was expressed from the pole of the left. There were two cervical glands outside the left tonsil, none on the right side. The temperature was 99, the pulse 120. A spinal puncture was made: the fluid was under pressure, and 10 c.c. were obtained. Cell count 83, globulin test + +. Ten c.c. of serum were given.

*Sept. 25.*—There was no extension of paralysis. The temperature and pulse were normal.

*Oct. 15.*—The right arm and left leg were still weak.

CASE 980.—W. K., a boy, aged fifteen months. (Patient of Dr. L. J. Porstman, Davenport, Iowa.)

*Sept. 24.*—The child had recently recovered from whooping-cough. He had been generally ill, with fever, vomiting, and fretfulness for the past three days. Tremors and jerky movements of various muscles during sleep had been noted from the beginning of the illness. There was marked weakness of the muscles of the neck, and difficulty in swallowing was noted the day before. *4 P. M.*—The muscles of the neck were completely paralyzed. The voice was extremely weak. The thorax was immobile, and the respirations were wholly diaphragmatic. Expansion of the diaphragm on the left side was limited; there was marked pallor and he was unable to swallow. A marked weakness was present in the arms and in the left leg. The temperature was 100.6. He was stuporous. A spinal puncture was made: the fluid was slightly turbid, and 10 c.c. were obtained. Cell count 347, globulin test + + +. Twelve c.c. of serum were given.

*Sept. 25, 9 A. M.*—The child was undoubtedly better, brighter

mentally, the voice was stronger, and he could move his head from side to side. There was definite expansion of the chest. The temperature was 99.6, the pulse 105. 1.30 P. M.—The condition was much changed. There was cyanosis, mucous rattle in the throat, and coarse mucous râles over the right lung posteriorly. The respirations were 60 per minute. The temperature was 103; the pulse was extremely rapid.

Sept. 26, 9 A. M.—The patient died.

CASE 983.—G. F., a girl, aged nine months. (Patient of Dr. F. O. Ringnell, Rock Island, Illinois.)

Sept. 25.—The child was cross, restless, irritable, and feverish two days before, but felt quite well the day before. Between 9 and 10 P. M. it was found that she could not hold up her head. There were marked jerking and tremor of the muscles of the left side of the body. Similar attacks occurred during the night. In the morning the left leg was weak and she was unable to move the right arm and the right leg. The temperature was 102.8. 4 P. M.—The head was retracted. She did not move the right arm and the right leg and they fell limply. The knee-jerk on the left side was exaggerated, and absent on the right side. The eyes turned to the left. A spinal puncture was made and 12 c.c. of fluid were obtained; the fluid was bloody but this was traumatic, due to difficulty in getting into the spinal canal. Six and one-half c.c. of serum were given.

Sept. 26, 3 P. M.—The mother said the baby rested quietly all the afternoon and night. In the morning the temperature was 102.5. She moved the right hand and leg, the latter with considerable strength. There was less rigidity of the neck. Attempts at flexion still caused pain. She looked brighter; the temperature was normal; 5 c.c. of serum were given. There was no extension of paralysis.

Oct. 15.—Marked improvement.

CASE 985.—J. B., a boy, aged three and three-fourth years. (Patient of Dr. P. H. Wessel, Moline, Illinois.)

Sept. 26.—Fever had developed during the night four days before. The child vomited the following evening, was constipated and had headache. There was jerking of various muscles of the body, pain in the right leg, and fever. He was very drowsy. Three days later (Sept. 26) there was marked weakness of the right leg. 2 P. M.—He complained of pain in the right leg and was unable to walk. The temperature was 100, the pulse rapid. A spinal puncture was made and 10 c.c. of fluid were obtained. Cell count 222, globulin test + + +. Ten c.c. of serum were given.

Sept. 27.—The temperature went to 102 during the night. In the morning the temperature was normal. The paralysis was not extended. Definite improvement had occurred in the power of the right leg.

Oct. 15.—Some weakness of the right leg was still present.

CASE 995.—I. R., a girl, aged eleven years. (Patient of Dr. L. F. Sullivan, Donahue, Iowa.)

*Sept. 27.*—The girl broke her right arm in a fall five days before. She felt ill, had a headache and some fever. There had been pain in the left leg for two days, thought to be due to the fall. 7 P. M.—The weakness of the left leg was marked and the neck was slightly rigid. The knee-jerks were absent. The temperature was 100.

*Sept. 28, 2.30 A. M.*—There was marked flaccid paralysis of legs and arms, she could barely rotate the left leg, and was unable to lift it in extended position. She was just able to lift the right foot from the bed with the knee partly flexed. She could not flex the left leg at the knee. There was marked weakness of the extensors and flexors of the left forearm and undoubted weakness of the right arm, but accurate tests could not be made on account of the fracture of the forearm. She could move the muscles of the arm but with very little strength. The knee-jerk and plantar reflex were absent on the left side; on the right side they were delayed but obtainable. A spinal puncture was made: the fluid was under moderate pressure, and 15 c.c. were obtained. Cell count 97, globulin test + +. Twenty c.c. of serum were given. 5.30 P. M.—No extension of paralysis had occurred. The right leg was possibly a little weaker. The grasping power of the left hand was undoubtedly greater than the night before. She could move her arms in all directions. Fifteen c.c. of serum were given.

*Sept. 29.*—Grasping power of the left hand was increased. The power of extension at left wrist was increased. The power of biceps, triceps, and deltoid muscles was also increased. The knee-jerk on the right side was obtainable, on the left absent. Plantar reflex on left side was obtainable. There was undoubted improvement in the strength of the right leg, but no change in the left. Ten c.c. of serum were given.

*Oct. 16.*—There was marked improvement, complete restoration of muscle power except in left leg, which also showed improvement.

CASE 1008.—C. G., a girl, aged eleven months. (Patient of Dr. G. T. Joyce, Rochester, Minnesota.)

*Oct. 12.*—Three days previously the child vomited and had a severe convulsion which lasted four hours. This was at first attributed to teething. She was extremely nervous and restless, and had jerky spells and twitchings of the muscles during the night and forenoon following the convulsions. She then became listless and drowsy, took no notice of things, and slept most of the time. A doubtful weakness of the right arm was first noticed twenty-four hours previously. 12 M.—There was undoubted weakness of the right arm and right leg and the muscles of the right side of the face. She could move both the right arm and the right leg but her strength was diminished. The knee-jerk on the right side was diminished, on the left side normal. There was a tendency to fall to the right when she sat up. The neck was rigid and attempts

to flex the head caused pain. 2 P. M.—There was undoubted extension of the paralysis. The right side of the face was more drawn, and there was no power whatever in the right arm and right leg. She was not able to pull the arm or leg away when the skin was pricked in giving the serum. She continued listless and took little notice of things. The tendency to fall to the right when sitting was more marked. The spinal fluid was clear and 2 c.c. were obtained. Cell count 8, globulin test + +. Ten c.c. of activated serum were injected intravenously. 7.30 P. M.—The right side of the face was less drawn. She appeared brighter, sat erect without falling to the right, and moved the right arm and leg. 9.30 P. M.—Improved. Ten c.c. of serum were given. The child had considerable power in the right forearm and succeeded in dislodging the needle from the small vein at the wrist in spite of the fact that the arm was held by a trained assistant. There was marked power in the right leg, making intravenous injection difficult.

The improvement after the injection of the serum was gradual. One month afterward the restoration of function of the muscles of the right leg, back, and the right side of the face was complete. Slight weakness of the right hand was still present but has since disappeared.

CASE 1024.—N. F., a boy, aged two years. (Patient of Dr. M. Bachman, Lake Park, Iowa.)

Nov. 3, 1917.—The illness began two weeks before with high fever, coryza, and a moderately sore throat. He had been constipated but did not vomit. He was hoarse and had fever for four days. The temperature was then normal. Marked weakness of the legs, especially the right, and the back began on the fourth day. Weakness of the right arm was first noted on the seventh day. There was little or no improvement, he could just stand, but cried from pain when made to take a step with support. He was pale, still very restless, cross, and irritable, and complained of pain in the legs. He cried out while asleep and was unable to roll over in bed. Pus was expressed from the left tonsil which was larger than the right. There were enlarged paratonsillar glands on the left side, none on the right. There was marked weakness of the right leg, the right knee-jerk was barely obtainable, the left normal. He could move the right arm in all directions but with impaired power. 4 P. M.—The spinal fluid was under pressure, clear, and 8 c.c. were obtained. Cell count 16, globulin test + +. Twelve c.c. of unactivated serum were injected intravenously.

Nov. 5.—The parents stated that the child slept soundly without waking for five hours following the injection of the serum. The pain had disappeared the day before. While lying down he kicked a hand with the leg in the extended position. He could walk and roll over in bed. He looked brighter and was more contented. The right knee-jerk was more active.

The improvement has continued, and complete recovery will probably take place.

every few minutes. The temperature was 104.2 by axilla. He was constipated and the bowel movement after an enema was very foul. The vomiting continued through the night.

*Aug. 19, 5 A. M.*—Axillary temperature 105, pulse 160. He was cyanotic, the respiration was short and rapid, and he was unable to swallow. Attempts to swallow water caused strangulation and convulsion. There was marked opisthotonos during the convulsion. He resisted having the head lifted forward, but the rigidity was not constant, the muscles relaxed at times, and the head came forward easily. He was semicomatose. The temperature reached 106 and the pulse was above 160. He vomited a large amount of coffee-ground material.

Death occurred from respiratory paralysis August 19, twenty-four hours after the onset.

**CASE 3.**—G. R., a boy, aged two years.

*Aug. 21.*—The child awoke with some fever. He was constipated and vomited once at noon. The temperature was 102, the pulse 140. He lay on his back and objected to being disturbed. There was tremor of the extremities, and he walked with a limp in the left leg. He complained of pain when the left leg and the head were moved. The left patellar reflex was absent, the right present; both plantar reflexes were present.

*Aug. 22.*—The temperature was 101.5, the pulse 140; breathing rapid. Paralysis of the left lower extremity was almost complete.

*Aug. 23.*—The temperature was 101 to 102. He was very restless, and cried out when moved. The pulse was rapid, the breathing rapid and short. The left leg was completely paralyzed, patellar and plantar reflexes of the right leg gone, but motion was still present.

*Aug. 24.*—Both lower extremities were completely paralyzed. There was very slight movement of the toes of the right foot when the sole of the foot was stroked. Urination was frequent. He was unable to hold his head up when it was raised.

*Later history.*—The fever continued 100 to 101 for six days after the paralysis was complete. The pulse was above 120 for four weeks, then gradually returned to normal. For three weeks he was restless and cried when moved. He slept very little at night.

*Oct. 17.*—To date there had been no improvement of either lower extremity. There was absolutely no motion in the left and only the minutest movement of the toes of the right foot with stroking of the plantar surface. He could with difficulty hold the head erect when the body was supported.

*Nov. 7.*—Death occurred from pneumonia.

**CASE 4.**—J. G., a boy, aged five years.

*Oct. 8.*—The temperature the evening before was 102. The child vomited and was constipated. He was not seen by a physician until 3 P. M., when he was semiconscious and cyanotic. The respiration was

60 and stertorous. He was restless and resisted having his head lifted forward. The patellar reflexes were gone, the plantar and triceps reflexes were present. There was no paralysis, but a spastic condition of the upper extremities. The temperature was 103, the pulse 160. During the examination the patient became distinctly worse. No sign of cranial nerve involvement could be detected, but because of the mental condition it was impossible to tell whether or not he could swallow or talk. A spinal puncture showed the fluid under slightly increased tension. Cell count 150, globulin test negative. A general examination failed to disclose any trouble in the chest or abdomen. The tonsils had been removed two weeks before.

Death occurred at 6 p. m., three hours after the diagnosis was made and twenty-four hours from onset of symptoms.

About one month previously I saw this patient as a suspected case with Dr. Weber. The symptoms at that time were due to tonsillitis, the attack resembling previous similar attacks.

### RESULTS

GROUP 4.—*Cases which occurred during the same epidemic, but in which the serum treatment was not given.*—Altogether there were 23 cases classified in this group. Nine of these patients died, a mortality of 35 per cent. If the 7 fatal cases were included in which the patients were moribund at the time of the serum treatment, there would be 16 deaths in the 30 cases, a mortality of 53 per cent. Complete data were not obtained in all of these cases, but in that available it was shown that the average age of the patients was five years; the onset was practically the same as in those who were treated; it was often acute, with high fever, rapid pulse, and severe gastro-intestinal symptoms. The incidence of paralysis in this group of patients was 100 per cent. Improvement in paralysis in those who lived was slow and slight as compared with those who received the serum treatment.

### DISCUSSION AND SUMMARY

Intravenous injections were made to the exclusion of intraspinal injections for the following reasons:

1. The best results were obtained by this method in the protection of monkeys against virus. The serum was activated for the same reason.

2. Invasion of the nervous system in poliomyelitis is only a part of a more or less generalized systemic infection (Flexner and his coworkers). This was particularly true in this epidemic. Infection of the tonsils,



the cervical and mesenteric lymph-glands, and the gastro-intestinal tract was often marked.

3. The spinal fluid in poliomyelitis is known not to contain the virus. The disease process is situated chiefly in the depths of the cord, which can best be reached through the circulation, particularly if lymph drainage toward the spinal canal is promoted by the withdrawal of spinal fluid.

4. Intraspinial injections of immune serum, human and horse, are known to be irritating and at times dangerous. They may produce, to quote Draper, "severe pictures of meningeal irritation, with vomiting, opisthotonos, and sometimes convulsions." Peabody warns against intraspinal injections in patients who have already developed paralysis. Moreover, intraspinal injections of serum increase the susceptibility of monkeys to intravenous inoculation of virus (Flexner and Amoss). Hence any good which follows intraspinal injections of immune serums occurs in spite of these primarily undesirable and at times probably harmful effects.

Altogether, 94 intravenous injections were made. In no instance was there a primary toxic action noticeable, and in only 6 (10 per cent) was there later evidence of serum disease. If the temperature was normal, no rise occurred; if above normal, an immediate drop without an initial rise was the rule, especially early in the disease. In this respect the action of the serum differed from that following intraspinal injection of immune human (Zingher, Amoss and Chesney, Draper, and Peabody) or immune horse serum (Nuzum and Willy) when, owing probably to the toxic action of the serum on the meninges there is often first an initial rise in temperature and then a drop.

The low incidence of serum disease in my series, 10 per cent, as compared with the incidence of 33 per cent in Nuzum and Willy's series, and apparently a more immediate beneficial effect, may be due (aside from an apparently more powerful serum, the agglutinating power being much higher, smaller doses being necessary to be effective) to the fact that intravenous injections only were given.

The exact mode of action of the serum is not definitely known. However, it is probably specific in nature and not due to non-specific effects, because normal horse serum and the serum of Horse 3 (with and without cresol) injected with strains which had lost their specific antigenic properties had little or no protecting power against virus in monkeys.

Altogether 58 patients with poliomyelitis, irrespective of the severity or type of the disease, were treated. Of these 10 died, a total mortality rate of 17 per cent. Excluding 7 of the fatal cases in which the patients were practically moribund at the time of the serum treatment, there were 3 deaths, a mortality of 6 per cent, in 51 cases in which the serum had a fair chance. This is in marked contrast to the 23 untreated cases, in which 9 patients died, a mortality of 35 per cent. Including the moribund patients as untreated, there were 16 deaths in 30, or a mortality of 53 per cent. That the patients treated in the early stages were undoubted cases of poliomyelitis is indicated by the symptoms, the increased pressure of spinal fluid, the cell count, the positive globulin test, and by the fact that in two cases, not poliomyelitis, in which spinal puncture was done, no cells were found in the spinal fluid, and the globulin test was negative. One of these was an emaciated baby nine months old with fever, vomiting, persistent diarrhea, green stools, and repeated convulsions. The other was a girl five years of age with severe headache, high fever, vomiting, full, rapid, and bounding pulse, and enlarged, acutely infected tonsils from which cheesy plugs were expressed. Moreover, the findings in these 2 cases are in accord with those of Wells, who has found few or no cells and no increase in globulin in the spinal fluid of patients presenting symptoms in common with acute poliomyelitis.

Paralysis did not develop in a single patient when treatment was begun before its onset, and all recovered. According to Draper (cited by Peabody), about 50 per cent of proved cases develop paralysis if untreated. A comparison of the results of the treatment of preparalytic cases by immune human and immune horse serum is of interest in this connection. Eighteen per cent of 54 patients treated by Zingher with immune human serum developed paralysis with no deaths. Twenty-nine per cent of the 14 patients treated by Amoss and Chesney developed paralysis and 14 per cent died. Thirty-one per cent of 51 patients treated in Peabody's series developed paralysis and 10 per cent died. None of 14 cases treated by Nuzum and Willy developed paralysis, but 1, or 7 per cent, died. In my series of 16 preparalytic cases none developed paralysis and none died.

No extension occurred following the giving of serum in the patients who recovered and in whom paralysis was marked at the time of the serum treatment. In only 3 or possibly 4 patients, or 8 per cent, receiving the serum will there be permanent impairment of function, and in all but one this will be slight. Wickman's 530 patients showed resid-

ual paralysis in 56 per cent one and one-half years later. Massachusetts records cited by Draper show a permanent paralysis of 83 per cent. The good effect was not due wholly to withdrawal of spinal fluid because the amount removed was relatively small in all cases and too small to have any possible effect in a number in each group which showed striking improvement.

The drawing of conclusions as to the exact value in this disease of any treatment is most difficult. Considering all the facts, however, the serum used appeared to have a prompt and powerful beneficial effect in a very large percentage of the patients treated. Its harmlessness, at least, is demonstrated and its use on a large scale indicated. The treatment should be given before paralysis has developed, hence early diagnosis by spinal puncture should be made. The course of this disease should be considered in terms of hours, not days, particularly now that there is available what appears to be a curative serum. The serum is of distinct benefit at least as long as postparalytic pains are present or the spinal fluid is positive. The strikingly favorable result (Case 1008) indicates that the serum will be of value in the treatment of sporadic poliomyelitis.

The fact that so many patients recovered completely in such a remarkably short time following injection of this serum indicates that the pleomorphic streptococcus is not merely a secondary invader but is in some way, as yet partially obscure, the cause of epidemic poliomyelitis.

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# TREATMENT OF ACUTE POLIOMYELITIS WITH IMMUNE HORSE SERUM

## Further Studies \*

E. C. ROSENOW

The demonstration that the somewhat peculiar streptococcus, isolated in poliomyelitis from time to time by various observers, has elective affinity for the central nervous system of young rabbits and guinea-pigs, producing symptoms and lesions resembling poliomyelitis in man,<sup>7</sup> indicated that this organism was no longer to be regarded as a mere secondary invader, but of real etiologic importance.

The possibility of developing a curative serum for poliomyelitis with this organism was first suggested in the experiments by Rosenow, Towne, and Wheeler,<sup>8</sup> in which monkeys were protected against injections of virulent virus, and experiments in the immunization of horses were instituted. These fundamental observations stimulated a reinvestigation of the etiology of poliomyelitis and of its treatment.<sup>12</sup>

The serum from a horse (Horse 1), injected with freshly isolated strains from experimental poliomyelitis in monkeys, was found to protect monkeys against inoculation of virus<sup>9</sup> (corroborated recently by Nuzum and Willy<sup>4</sup>), to have definite curative effects in monkeys after the onset of paralysis, and apparently a powerful curative action in poliomyelitis in man. In a preliminary report<sup>10</sup> on the treatment of 44 cases these statements appear:

All of the 16 patients treated before paralysis had begun recovered without paralysis. . . . The apparent good effects from the injection of serum are often striking. The headache, nervousness, restlessness, and tremor often disappear promptly. The temperature and pulse-rate are lowered. A beginning paralysis often disappears in an astonishingly short time. A rapidly progressing paralysis is often arrested and improvement is unusually rapid. The postparalytic pains do not appear or are comparatively mild.

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Nuzum and Willy<sup>5</sup> have since reported similar apparently striking benefits in a large series of cases following the use of an immune horse serum prepared in a similar manner.

The further results given in the detailed report<sup>11</sup> on the treatment of 58 cases indicate that the serum has definite curative action in epidemic poliomyelitis. The series included one case of sporadic poliomyelitis in which equally good effects were noted.

It is my purpose to report in detail in this paper the results obtained in a number of cases of sporadic poliomyelitis, to record experiments on the use of the serum in experimental poliomyelitis in the rabbit, and to emphasize the importance of early diagnosis of this disease.

The serum used in the cases here reported, as in the series of cases of epidemic poliomyelitis, was injected intravenously and not intraspinally, as it had been found that intravenous injections were necessary to protect monkeys against intracerebral inoculations of virus.<sup>9</sup> Intraspinally injections of horse serum, as has been shown by Flexner and Amoss,<sup>3</sup> increase markedly the susceptibility of monkeys to poliomyelitis—so much so as to render them susceptible to intravenous injections of virus. The largely negative results, as reported by Amoss and Eberson,<sup>1</sup> on the therapeutic power of my serum in monkeys, would appear to be due to the fact that they gave exclusively intraspinal injections instead of intravenous injections. To facilitate slow injection (1 c.c. per minute) the serum was diluted with an equal quantity of salt solution, but was not activated with guinea-pig complement.

## REPORT OF CASES

### *Cases in which there was Slight Paralysis at the Time of Serum Treatment*

CASE 1 (1042).—E. T. P., a boy, aged nineteen months, a patient of Dr. C. T. Granger, Rochester, Minn., seen Dec. 23, 1917, had been fussy for a few days, owing, it was believed, to teething, since two teeth were in the process of eruption. For two weeks the patient's two sisters had had colds, running of the nose and cough, but they were apparently free from fever. During the previous night the child had been restless; he slept at intervals, but frequently awakened. There was no noticeable fever. He had had two loose, foul-smelling stools the day previously, but there was no vomiting. During the night a weakness of the muscles of the neck was noticed, the child being scarcely able to hold up his head. At 10 A. M. he was found lying on a couch with the head retracted, eyes partly open, and with frequent twitchings

of the right arm and legs. On being aroused he showed a decided mental apathy, marked tremor and ataxia, and rigidity at the neck. The face was symmetric. The tongue protruded slightly to the left. He was able to stand and to hold the head erect, but was unable to get up unassisted, and in sitting down repeatedly fell to the floor quite limp. The left knee-jerk was normal, the right was exaggerated, and the reflexes of the upper extremities were normal. The temperature was 100.4. When a spinal puncture was made, the weakness of the legs and muscles of the back became very noticeable. The spinal fluid spurted, and 10 c.c. were withdrawn; but owing to the presence of traumatic blood, a cell count and globulin test could not be made. A differential cell count, made of a stained specimen of the sediment, showed 70 per cent mononuclear cells. Ten c.c. of serum were injected. The child slept quietly for three hours after the serum was given, and with less twitching of the muscles. At 5 p. m. the temperature was 100. He looked brighter, sat up, and stood without tremor. Retraction and rigidity of the neck less marked, but still evident. He was able to get up from a lying position unassisted, and walked readily, but was still somewhat weak and unsteady. The tongue protruded in the median line. There was no weakness of the arms. The knee-jerks had become normal and equal.

*Dec. 24, 1 P. M.*—The child looked brighter, and tremor and tremulousness had disappeared. He had slept well during the night. He sat up unassisted, and stood and walked without support, but there was still some weakness of the muscles of the back, noticeable when he was sitting down. The temperature was normal, the face symmetric, the tongue protruded in the median line, and the retraction and rigidity of the neck were absent. The knee-jerks were normal. Eight c.c. of serum were injected.

*Dec. 25.*—No weakness could be made out. The child appeared well. Recovery was complete.

CASE 2 (2008).—L. R. B., a boy, aged two years, a patient of Dr. G. T. Joyce, Rochester, Minn., April 3, 1918, at about 2 o'clock in the afternoon, was acting peculiarly; he was fussy, and it was discovered that he was unable to walk on account of weakness in the legs. He had had diarrhea the day previously, with four or five watery stools of extremely foul odor. There was no apparent fever, but a cough developed during the morning, as a result, presumably, of exposures to whooping-cough three weeks and ten days previously. At 9.30 p. m. the child was entirely unable to bear weight on the legs, and in repeated efforts to do so the legs gave way at the knees; the left leg was weaker than the right. There was no swelling of the joints, and no complaint of pain. The child was well nourished. The left knee-jerk was barely obtainable, the right only slightly diminished. The spinal fluid was under increased pressure, was clear, and 6 c.c. were withdrawn. The

cell count was 21, the globulin test was strongly positive, flocculation occurring almost immediately. Twelve c.c. of serum were injected.

*April 4, 8.30 A. M.*—After the child had slept all night, without restlessness, turning over in bed normally a number of times during the night, there was no tremor, he looked well and could walk without support, but some weakness of the legs was still evident. Knee-jerks were normal. The injection of serum was repeated. At 9 p. m. the child walked readily without assistance and without apparent weakness. The reflexes were normal, and he appeared well in every respect. Recovery was complete.

*Case Showing Advanced Progressing Paralysis at the Time of Serum Treatment*

CASE 3 (1078).—C. A., a boy, aged two years, a patient of Dr. G. T. Joyce, Rochester, Minn., Feb. 24, 1918, was weak, poorly nourished, pale, and had had several attacks of severe anemia. He had been fussy, cross, feverish, and irritable for two days. He had not walked normally and had fallen easily, once from the doorstep, the day previously. He vomited repeatedly during the morning and was feverish, but had no diarrhea. Mumps was epidemic in the neighborhood; the mother had it three weeks previously, and the fever and illness of the child were thought to be due to mumps because there was a swelling in the region of the left parotid. At 6 o'clock he had severe convulsive seizures with marked spasms of the right side of the face, the right eye, and the right arm, but also spasms and twitchings of the muscles of the left side. The right arm became completely helpless within one hour. At 10.30 p. m. there was moderate swelling in the region of the left parotid, a complete flaccid paralysis of the right arm, which dropped limply to the side when lifted, and inability to close the right eye. The right side of the face was drawn markedly, especially when the child cried. There was weakness of the muscles of the right side of the neck, the head tending to fall forward and to the left. He could just stand, but was unable to get up alone. There was moderate retraction and rigidity of the neck and weakness of the right leg, and the right foot was rotated outward. Attempts at flexion of the head caused severe pain. The knee-jerks were exaggerated; the reflexes in the right forearm were barely obtainable, and the triceps and biceps reflexes were absent. The temperature was 97, and the pulse was rapid. The child took no interest in his surroundings and cried apathetically when handled; but as soon as left alone he went back into a semicomatose sleep. The spinal fluid was under increased pressure. Eight c.c. of slightly turbid fluid were withdrawn. The cell count was 550, and the globulin test strongly positive. The Wassermann test of the spinal fluid proved negative. Twelve c.c. of serum were injected.

*Feb. 25, 9 A. M.*—After a quiet night the child closed the right eye

readily and appeared brighter, but complained of pain in the left foot. The face was less drawn. The reflexes were stronger and the biceps and triceps reflexes were easily obtainable. The strength in the right arm was decidedly greater; he could lift it from the bed in turning over, and offered decided resistance when it was moved. Ten c.c. of serum were injected. At 8 p. m. the temperature was 98. The child had been restless for several hours after the serum was given, moving the right arm markedly four times during the afternoon. He slept naturally, with face symmetric and with both eyes closed. The swelling of the left parotid was more marked, he appeared brighter, and took an interest in his surroundings. The face was less drawn when he cried and the head was held erect. There was no rigidity of the neck, the arm and forearm were moved, and the fingers were flexed quite vigorously on repeated tests. The knee-jerks and the reflexes of the right arm and forearm were normal. Ten c.c. of serum were given.

*Feb. 26, 9 A. M.*—It was reported that the child had slept well and eaten breakfast with relish. The swelling in the left cheek had diminished, the face was symmetric when at rest and only slightly asymmetric when he cried. The right arm was moved with considerable power. Ten c.c. of serum were injected. At 8 p. m. the right arm was decidedly stronger.

*Feb. 27, 8 A. M.*—The condition was about the same as the night before. At 8 p. m. the child was about the same, but had been more fussy and cross during the afternoon.

*Feb. 28, 9 A. M.*—There was no improvement in the condition. At 9 p. m. the condition had not improved. The child complained of pain in the right leg during the afternoon, and was unable to walk unassisted. Ten c.c. of serum were given.

*March 1, 9 A. M.*—The child was able to walk and get up on his feet unassisted; he appeared brighter, the face was less drawn, the eyes closed completely, and power in the right arm was decidedly greater. Ten c.c. of serum were given. At 8 p. m. there was decided improvement in the power of the right arm; the reflexes were normal.

*March 2, 8 A. M.*—The child walked without apparent weakness in the legs. The face was symmetric. The strength in the shoulder group of muscles on the right side was decidedly improved; the reflexes were normal.

*March 10, 8 P. M.*—The child appeared well. The power in the right arm was quite marked; he grasped fingers with vigor, but used the hand little. He walked without limp. The face was symmetric, with no swelling of the left parotid gland. He broke his right leg, which was placed in a cast, and further observations were temporarily interfered with.

*June 3.*—The child looked puny and poorly nourished. The face was symmetric. He moved the right arm in every direction, but the extensors of the fingers were still weak. There was slight dragging of



the right foot, but he walked without apparent weakness in the leg or back. The reflexes were normal.

*Case Showing Marked Paralysis Ten Days After Onset*

CASE 4 (1024).—N. F., a boy aged two years, a patient of Dr. Morris Bachman, Lake Park, Iowa, and of the Mayo Clinic, had been taken sick two weeks previously with a high fever which lasted four days.

Nov. 3, 1917.—There was a slight soreness of the throat and stiffness of the neck; there was no vomiting or diarrhea, but marked constipation. On the fourth day the child developed marked weakness in the muscles of the legs and back, and on the seventh day, weakness of the right arm. On examination pus was expressed from the left tonsil, which was larger than the right, and an enlarged peritonsillar gland was found on the left side, but none on the right. The child showed a marked disinclination to walk, and complained of pains in the legs. He was still very restless and irritable, and awakened at night, calling out in his sleep. Power in the legs had increased definitely, but there was marked weakness in the right leg, the right arm, and the muscles of the back. The right knee-jerk was barely obtainable and the left was normal. The child could move the right arm in all directions, but with impaired power. At 10 A. M. a spinal puncture revealed spinal fluid under moderate pressure, and 5 c.c. were withdrawn. The cell count was 16, the globulin test markedly positive. Twelve c.c. of serum were injected.

Nov. 4.—He had slept for five hours without waking, following the injection of serum, but had a restless night.

Nov. 5.—He slept soundly through the night without waking, for the first time since he became ill. He looked brighter and was much less fussy, the disinclination to walk had disappeared, and he no longer complained of pain in the right leg. He was able to roll over in bed and with the right foot could kick a hand held above the bed, neither of which he could do the day previously.

Dec. 18.—The child was perfectly well, walking and running without recognizable limp. The reflexes were normal.

*Case of Doubtful Diagnosis*

CASE 5 (1056).—O. I. J., a girl, aged two years, a patient of Dr. George Stevens, Byron, Minn., ten days previously had gone to bed perfectly well, and the following morning a slight limp was noted in the right leg, which persisted.

Jan. 15, 1918.—There was pain in the region of the right knee and the outer aspect of the right leg was complained of. The temperature was 100. A cough had developed, due to a cold; the mother also had a cold. There was a doubtful tendency to toedrop on the right side. The child appeared quite well. The reflexes were normal; there were no twitchings, retraction, or rigidity of the neck and no pain in the

back on flexion. The tonsils were large, and the crypts were filled with numerous quite hard, brownish-gray plugs which could be easily expressed. There were no palpable glands in the neck. Spinal puncture revealed fluid under normal pressure, and 4 c.c. of clear fluid were withdrawn which was negative for cells and globulin test. Twelve and five-tenths c.c. of serum were injected.

*Jan. 16.*—There was no change in the condition.

*Jan. 18.*—The child limped a little. Recovery was complete.

### *Case of Tuberculous Meningitis*

CASE 6 (1095).—M. O., a girl, aged eight years, a patient of Dr. G. O. Fortney, Zumbrota, Minn., and of the Mayo Clinic, seen March 17, 1918, had complained of pain in the right hip, in the fall of 1917, especially at night, and soon developed a limp and pain on walking, which gradually progressed until February, 1918, when she was placed in a cast. One week previously she complained of constant headache, pain in the back, and photophobia. There was loss of appetite and vomiting of everything taken. The morning temperature was 101; the afternoon temperature was 99, and the pulse was slow.

*March 19.*—The spinal fluid was clear, the cell count 178, and the globulin test positive.

*March 20.*—Cultures from the spinal fluid in glucose broth showed pure culture of short-chained streptococcus. The patient was stuporous and apathetic, and was unable to open her eyes more than 1 cm., the upper lids dropping, the right more than the left. There was undoubted weakness in the muscles of the right side of the face, manifested as the patient showed her teeth. There was no nystagmus. The tongue was tremulous, but protruded in the median line. The triceps and biceps reflexes on both sides were absent. Knee-jerks were present. There was decided rigidity of the neck. Grasping power in both hands was slight, but she could move her arms in all directions. At 2 P. M., owing to the finding of the streptococcus in the spinal fluid and the beginning of paralysis in the muscles of the face and upper extremities, 25 c.c. of serum were injected intravenously. At 3.20 P. M. she had a decided chill, the pulse was 120, and there were two degrees of rise in temperature, but no other change.

*March 21.*—The general condition remained about the same; the left eyelid drooped decidedly, and the weakness in the arms had grown more marked. The blood-agar plate of the culture obtained from the spinal fluid showed countless numbers of indifferent colonies of streptococci, which were not agglutinated by poliomyelitis serum. A second culture of the spinal fluid proved negative.

*March 22.*—The patient was stuporous. There was ptosis of the left eyelid; both pupils were dilated and did not react to light. She did not move the right arm, and still evinced dislike to being touched

or examined. The rigidity of the neck was more marked, and there was slight opisthotonos. Death occurred at 10.25 P. M. The findings at necropsy were typical of tuberculous meningitis.

#### SUMMARY OF CASES

The two patients (Cases 1 and 2) that were treated before marked paralysis had occurred showed the most striking benefit, as did those in the epidemic form of the disease, both recovering completely within forty-eight hours. The result in the child with mumps (Case 3), who was markedly under size, anemic, and poorly nourished, who had convulsions followed by an extensive weakness on the right side of the body, and complete paralysis of the right arm, and a high cell count in the spinal fluid, was less striking, but unmistakable improvement followed each injection. The patient (Case 4) in whom the serum was given ten days after the onset of paralysis likewise appeared benefited. In Case 5, in which the diagnosis was very doubtful, and in Case 6, which proved to be tuberculous meningitis, the results, as was to be expected, were indifferent.

The primary culture from the pus from the tonsil of Case 1 was injected into one rabbit, which died with marked invasion of the central nervous system, and from which a pure culture of the characteristic streptococcus was isolated.

In the earlier work on elective localization it was the rule to inject the streptococcus from poliomyelitis soon after its isolation. In order to determine whether the peculiar localizing power could be maintained through many subcultures, and thus rule out all possibility of carrying over "virus," subcultures in glucose brain broth were made from every three to eight hours, and the nineteenth culture generation was injected intravenously in rabbits. All but three of ten rabbits developed paralysis or showed elective localization.

The symptoms in the rabbit following injection of these strains are usually marked and progress rapidly, the animals dying in convulsions or from paralysis of the muscles of respiration. The amount of infiltration in the nervous system is mild as compared with that in man and in the monkey.

These conditions were thought favorable to test the efficacy of the serum, and a series of rabbits which showed paralysis were treated with it. The rabbits seemingly derived marked benefit. Injections of normal horse serum had no apparent effect.

## REPORTS OF TWO ILLUSTRATIVE EXPERIMENTS

*Experiment 1.*—Rabbit 1477, weighing 1009 gm., was injected intravenously Jan. 8, 1918, with 7 c.c. of glucose brain broth culture, in the nineteenth subculture after one animal passage.

*Jan. 10, 3 P. M.*—The animal was found in the cage apparently quite well, but there was continuous fine tremor of the muscles of the whole body, frequent twitching, and mild clonic spasms of the muscles of the neck. It was extremely hyperesthetic, and the head was slightly retracted at times. When it was placed on a smooth surface, undoubted weakness of the anterior extremities was noted, particularly in the adductors (Fig. 263). Respirations were rapid, and there was marked salivation. The temperature was 104.8. At 3.20 P. M. the weakness in the anterior extremities was more marked; the tremor and spasms were less marked in the anterior extremities, but extended to the hind extremities, and the paralysis was rapidly increasing. The animal was entirely unable to bear its weight on the front extremities and had difficulty in getting its hind legs under the body. Tremor was markedly increased when it was lifted from the cage. At 3.45 P. M. 1 c.c. of serum from Horse 1, with an equal quantity of salt solution, was injected intravenously. At 4.20 P. M. there was less weakness, and tremor and spasms were limited



Fig. 263.—Rabbit 1477, showing marked weakness of fore extremities forty-eight hours after the intravenous injection of the culture from the tonsil in Case 1 after one animal passage.

limited to the muscles of the head. The front legs were undoubtedly stronger and did not spread out as much in walking on a smooth surface. Salivation was less marked. The temperature was 105. The injection of serum was repeated. At 4.45 P. M. the tremor was limited to the muscles of the jaw and neck; the fore extremities were stronger, and there was much less tremor when it was lifted from the basket. The fore legs spread slightly; the weakness in the hind legs was less marked. Salivation was absent. At 5.15 P. M. the picture had entirely changed; the animal was eating carrot and walked without difficulty and without evidence of weakness. Tremor was entirely absent, and the respirations were diminished. At 6 P. M. it appeared quite well. Salivation and tremor were entirely absent. There was slight twitching of the muscles of the front legs when it was lifted from the basket. It walked normally on a smooth surface. The respirations were nearly normal. The

temperature was 103.6. At 7 P. M. it appeared well, the respirations were normal, and salivation and tremor were absent even when it was lifted from the basket. It walked without manifest weakness. There was no retraction of the head. The temperature was 101.8. At 7.30 P. M. it appeared well, and jumped from a platform 2 feet high without evidence of weakness in the extremities while a moving picture was being taken. At 9 P. M. the animal ate carrot with relish (Fig. 264) and jumped out of the basket and ran about on the floor normally, without tremor. There was no hyperesthesia.

*Jan. 11, 6.45 A. M.*—The animal had escaped from the basket and was found running about on the floor, apparently perfectly well with no sign of weakness anywhere. It was hungry and ate carrot ravenously.



Fig. 264.—Rabbit shown in Fig. 263 five hours after serum treatment.

It was observed all day and appeared well, with no sign of return of symptoms.

*Jan. 12, 7.30 A. M.*—The animal appeared well. At 12 M. a decided tremor of the head and fore extremities was noted when it was lifted from the basket, but no weakness of the extremities was evident. At 2.20 P. M. the tremor had become decidedly more marked. The serum injection was repeated. At 6 P. M. it appeared well; there was no tremor on handling, and no weakness. At 9 P. M. the condition was unchanged.

*Jan. 19.*—The animal was perfectly well and active, with no sign of weakness anywhere. It remained perfectly well until May 2, when it died from snuffles, which was epidemic in the laboratory at that time.

*Experiment 2.*—Rabbit 1481, weighing 1060 gm., was injected Jan. 11, 1918, the same as Rabbit 1477.

*Jan. 12.*—The animal appeared well.

*Jan. 17.*—The animal appeared well and was injected intravenously with a six-hour culture in glucose-brain broth of the same strain after two animal passages.

*Jan. 18.*—There was undoubted weakness of the left foreleg, which went into spasm in the extended position when the animal was lifted by the ears. Both forelegs spread out widely when it was placed on a smooth surface, the left more marked than the right. There was no tremor.

*Jan. 19.*—There was marked extensor and adductor weakness of the forelegs, especially the left, and slight tremor of the anterior part of the body but no retraction of the head.

*Jan. 20, 11 A. M.*—The animal was scarcely able to extend the front paws. Both legs tended to spread out widely in an attempt to stand on a smooth surface. The anterior part of the body trembled



Fig. 265.—Rabbit 1481, showing marked weakness of all extremities nine days after the first and two days after the second injection of the same strain after two animal passages.

markedly in the attempt to walk, but there was no apparent weakness in the hind legs. There was marked loss in weight. At 1 p. m. weakness was more marked in the anterior extremities. At 5.30 p. m. the condition was worse, the animal being just able to bear weight on the front extremities. There were tremor and a tendency to spasm of the hind legs, with some difficulty in maintaining balance, and evidence of weakness in the muscles of the hind extremities. At 6.30 p. m. the paralysis was rapidly growing worse, the animal was unable to get its hind legs under it after they were extended, and it was entirely unable to bear weight on the front or hind extremities when on a smooth surface. The respirations were shallow, irregular, and almost entirely abdominal. The ears were cold and drooped markedly (Fig. 265). The temperature was 100.8. One c.c. of serum of Horse 1 and 1 c.c. of salt solution were injected intravenously. After the injection the animal was placed in a cage, utterly unable to walk or stand. At 7.30 p. m. it was found in

the opposite corner of the cage,  $2\frac{1}{2}$  feet from the place where it was left an hour previously. It stood with the chest from the floor of the cage, and was just able to walk. The temperature was 101. There was a tendency to spasm of the hind legs when it was lifted from the cage. The injection of serum was repeated. At 8 P. M. it was found hopping about in the cage, and it ate greens with relish. The respirations had become regular, and expansions of the chest had become greater. At 9 P. M. it was hopping about in the cage and ate greens and oats. On being placed on a smooth surface it was able to stand erect without the paws slipping from under it, and it walked about with little weakness except the extensor weakness of the left paw. The power of the muscles in the ears had returned. The respirations were normal, and there was



Fig. 266.—Rabbit shown in Fig. 265 fourteen hours after serum treatment.

no tremor. The temperature was 102. The injection of serum was repeated.

*Jan. 21, 7.15 A. M.*—It appeared well, ate carrot with a relish, and hopped about the cage quite normally. When it was placed on a smooth surface, no weakness could be demonstrated (Fig. 266). There was sufficient strength to raise the weight of the body in its attempts to get on the top of a microscope case. It ate normally, its ears no longer drooped, the respirations were normal, and the temperature was 101. The animal appeared perfectly well until January 25, when it was found dead. There were no lesions of the central nervous system, cultures of the brain and cord were negative, and the liver showed marked coccidiosis.

#### CONCLUSIONS

The results in acute sporadic poliomyelitis, as in the epidemic form of the disease, and in experimental poliomyelitis in the rabbit, are so strikingly favorable as to leave little doubt regarding the value of this

treatment. Therefore, the importance of recognizing poliomyelitis early is evident, as it never has been heretofore.

It cannot be too strongly emphasized that this disease has quite a characteristic syndrome, as has been emphasized by Draper,<sup>2</sup> Peabody,<sup>6</sup> and others, which should lead to its tentative diagnosis, and to the immediate making of spinal puncture for conclusive diagnostic tests. If a patient has symptoms which suggest involvement of the central nervous system and shows an increased amount of spinal fluid, an increased number of cells with mononuclears predominating, and a positive globulin test, the serum should be administered immediately. If further study should prove the symptoms due to some cause other than poliomyelitis, no harm will have been done, while if the treatment is delayed, irreparable harm may occur.

It is realized that a large number of patients must be treated before final conclusions can be drawn. Since the sporadic form appears also to yield to the treatment, there should be a supply of the serum in the hands of many.

A large amount of serum, believed to be as effective as that used thus far, is on hand, and will be sent gratis to any one who has an opportunity to use it, and who will furnish records of cases.

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12. The reader is referred to a series of papers by the writer and his associates that appeared in the April number of the *Journal of Infectious Diseases*, 1918, xxii, 281-426. In these papers, contributions by other observers are discussed.



# THE DEMONSTRATION OF IMMUNE OPSONINS FOR THE PLEOMORPHIC STREPTOCOCCUS IN EXPERIMENTAL POLIOMYELITIS IN MONKEYS\*

WILLA M. DAVIS

Rosenow, Towne and Wheeler, Mathers, Nuzum and Herzog, and Kolmer, Brown and Freese, have described a micrococcus isolated quite constantly from brain and cord in cases of acute poliomyelitis, and Rosenow and Towne have isolated a similar organism from paralyzed monkeys following injection of virus. Mathers and Tunncliffe found an increase in opsonin apparently specific for this micrococcus in the serum of patients during the attack of poliomyelitis. Mathers and Howell found a specific increase in opsonin in the serum of rabbits immunized with different strains of the pleomorphic streptococcus. Kolmer and Freese, using polyvalent antigens of this streptococcus, found a positive complement-fixation reaction with the serum of a small percentage of persons with poliomyelitis. Solis-Cohen and Heist found "that the serums of a large percentage of patients with poliomyelitis give high opsonic indexes with this streptococcus, but not with streptococci from non-poliomyelitic sources nor with staphylococci, diphtheroids, and Gram-negative bacilli obtained from poliomyelitic material."

In an extensive study of the question of antibody production in poliomyelitis, Rosenow and Gray found an increase in the specific agglutinating power toward this organism in the serum of patients with poliomyelitis, in the serum of monkeys with poliomyelitis following inoculation of virus in the usual way, and in the serum of monkeys injected with the "poliococcus." The present study concerns the development of immune opsonins in the serum of monkeys following the inoculation of active poliomyelitis virus. Four monkeys were used in the experiment.

Monkey 147, a normal control, was not injected.

\* Reprinted from *Jour. Infect. Dis.*, 1919, xxiv, 176-180.

Monkey 148, April 21, 1917, was given 0.5 c.c. of a 5 per cent saline suspension of glycerinated virus intracerebrally. April 28 the animal showed paralysis; it died April 29. The lesions were characteristic and the pleomorphic streptococcus was isolated from brain and cord.

Monkey 149, April 21, 1917, was given .5 c.c. of sensitized vaccine intravenously. The dose contained the pleomorphic streptococcus from 75 c.c. of dextrose broth culture. Previously the organisms had been suspended in immune horse serum for two hours at 37° C., after which they had been left in the ice-box over night. They were then washed in water and suspended in salt solution.

Monkey 150, April 21, 1917, was given 20 c.c. of normal horse serum intravenously to demonstrate whether the horse serum alone would produce any increase in opsonin. May 2, four days after the death of Monkey 148, Monkey 150 was given 0.5 c.c. of a 5 per cent saline suspension of glycerinated virus intracerebrally, and in addition an intravenous injection of 12 c.c. of immune horse serum. The intravenous injection of 12 c.c. of immune horse serum was repeated May 3, 5, 6, and 7. May 8 the animal showed definite flaccid paralysis and died May 14. The lesions were characteristic; the results of the cultures were similar to those from Monkey 148.

Blood was collected from these four monkeys April 18 and every second day thereafter until April 29, when the paralyzed monkey died. The blood was allowed to clot, placed in the ice-chest for twenty-four hours, and after the serum had been decanted it was stored in the ice-box until June, when the counts were made.

#### TECHNIC

The strains of the pleomorphic streptococci used in this study had previously been proved to have retained their specific agglutinating property. They came from human cases of epidemic poliomyelitis occurring in New York and Philadelphia, and from monkeys paralyzed by the injection of virus. Eight of the human strains (714, 721, 722, 729, 839, 841, 842, 899) were recovered from the brain and cord and 3 (730, 732, 748) from the tonsils. The 3 monkey strains (M49, M106, M148) were recovered from the brain and cord of monkeys paralyzed with virus or filtrates of virus. The exponents to the right and above the figures designating the strain in Tables 1 and 2 indicate the number of animal passages; the figure following the period designates the culture generation. Three control strains were used—a *Streptococcus*

viridans from the tonsil in a case of arthritis, a pneumococcus (622), and a slightly hemolyzing streptococcus (257).

Most of these strains had been kept in the laboratory in deep stabs of ascites fluid, plain tissue agar, and were transferred to bouillon twenty-four hours before the counts were made. Any broth cultures in which the growth was not uniformly diffuse were discarded.

The test-tube method was used in making the opsonin determinations. The tubes containing 0.05 c.c. each of leukocyte suspension, serum, and culture were incubated at 37° C. for fifteen minutes, after which the smears were made immediately. The organisms in 50 leukocytes were counted; the figures in the tables, therefore, represent the actual number of organisms taken up by 50 leukocytes. Any cell which contained more than 30 organisms was not included in the count. Almost without exception these crowded leukocytes were found in mixtures containing immune serum.

The bacterial counts made are tabulated in series—two series in Table 1 and three in Table 2. As the same twenty-four-hour culture and the same leukocyte suspension were employed throughout, the conditions for each single series were uniform.

In Table 1 is given the opsonic power of the serum of four monkeys obtained in two series of experiments. The serum of the normal control, Monkey 147, and the one injected with normal horse serum, Monkey 150, in no case shows any increased opsonic power. On the other hand, the opsonic power of the serum of Monkey 148, injected with virus, and Monkey 149, injected with sensitized vaccine, shows a well-marked increase in phagocytic power eight days after injection against all of seven human strains of the pleomorphic streptococcus (3 before and 4 after from one to four animal passages) and 1 monkey strain, but no increase against the control strains.

In Table 2 are given the results obtained in three additional series of experiments. In this series, as in those shown in Table 1, the opsonic power of the serum of the normal control (Monkey 147) and Monkey 150 varied only slightly. The serum of Monkey 148 again shows a marked increased opsonic power after injection and after paralysis occurred. The increase is slight up to the sixth day after the injection of virus, but decided between the sixth and eighth days. The serum of Monkey 149 shows a consistent increase in opsonic power with all of 9 strains fourteen days after the injection of sensitized vaccine. It is of interest to note that this monkey showed a degree of immunity to virus in that the incubation period was prolonged for one week and the animal recovered, while the control died promptly after the onset of paralysis.

TABLE 1

STRAIN	OPSONIC POWER OF THE SERUM OF FOUR MONKEYS							
	Monkey 147 Normal control		Monkey 148 Injected with virus		Monkey 149 Injected with sensitized vaccine		Monkey 150 Injected with normal horse serum	
			Before injection		Before injection		Before injection	
	April 18	April 29	April 18	April 29	April 18	April 29	April 18	April 29
899.....	51	50	39	257	32	65	61	56
M 106.5.....	38	2	14	120	0	68	0	4
722 <sup>2</sup> .4.....	56	20	20	91	22	119	66	54
730.11.....	87	59	39	139	19	78	55	54
913 control.....	17	..	19	12	47	51	10	10
714.3.....	..	..	2	43	9	57	17	6
714 <sup>3</sup> .2.....	..	..	22	64	20	91	64	32
714 <sup>4</sup> .2.....	..	..	0	20	10	35	4	4
748 <sup>2</sup> .4.....	..	..	30	64	18	30	14	12
632 control.....	..	..	34	38	32	24	10	11

Eight days after  
injection; one  
day after onset  
of paralysis



The serum of Monkey 150 showed no change in opsonic power in numerous tests until twelve days after an intracerebral injection of virus and after repeated injections of immune horse serum. At this time there was a marked rise toward all of five strains (Table 2), and coincident with this marked increase in opsonin the animal showed a degree of immunity to virus, since it lived for six days after the onset of paralysis, while the control died of a rapidly progressing paralysis in twenty-four hours. It has previously been observed that immune horse serum does not always protect completely against the forced experiment of intracerebral inoculation of highly virulent virus. The lack of complete protection in Monkey 150 may, however, be due to the fact that the immune horse serum may have been toxic, since the animal received an injection of normal horse serum twelve days previously. (Tables 1 and 2.)

### CONCLUSIONS

There occurs a well-marked specific increase in opsonin for the pleomorphic streptococcus in the serum of monkeys during attacks of poliomyelitis following the inoculation of virus. Since this increase in opsonin occurs toward strains derived from human cases, as well as from experimental poliomyelitis following the injection of virus, the pleomorphic streptococcus in this disease cannot be regarded as an accidental invader of the nervous system.

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## THE USE OF CELLULOID IN THE CORRECTION OF NASAL DEFORMITIES\*

G. B. NEW

For many years it has been the general practice to use a piece of bone from the tibia, rib, or scapula, or a piece of cartilage from a rib, for an autogenous transplant in the correction of deformities of the nose resulting from trauma or syphilis. In carrying out this method the wound necessarily made where the transplant is taken causes more inconvenience to the patient than does the nasal wound.

During the past year I have used celluloid as an implant into the tissue over the nose in a series of dogs and in five cases in man. The results have been so satisfactory that the use of celluloid seems preferable



Fig. 267 (Dog B 684).—Piece of celluloid unaltered after being in tissue over dog's nose for one year.

to that of cartilage or bone. The necessity of taking a transplant is thereby eliminated and the operation simplified.

In 1908, Koschier reported two cases of nasal deformity in which he used thin celluloid plates, and he believes that this is the best heteroplastic material for the purpose. Koschier followed the method suggested by Föderl, who reported two cases in 1903 in which this material had been used. In 1916 Higgins recommended the use of celluloid in plastic surgery of the face. He has built up three noses with good results, and believes celluloid ideal material in such cases. He has used a fluid preparation of celluloid in elevating deep scars. Thompson, also

\* Reprinted from Jour. Am. Med. Assn., 1918, lxx, 988-990.

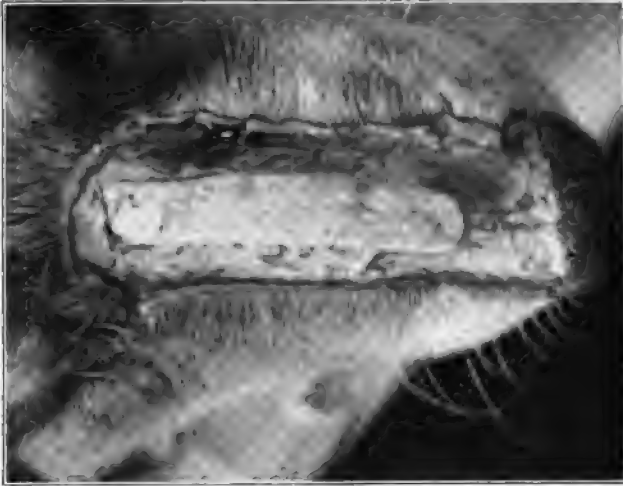


Fig. 268 (Dog B 684).—Celluloid in situ over dog's nose covered by subcutaneous tissue. Small area of celluloid exposed.

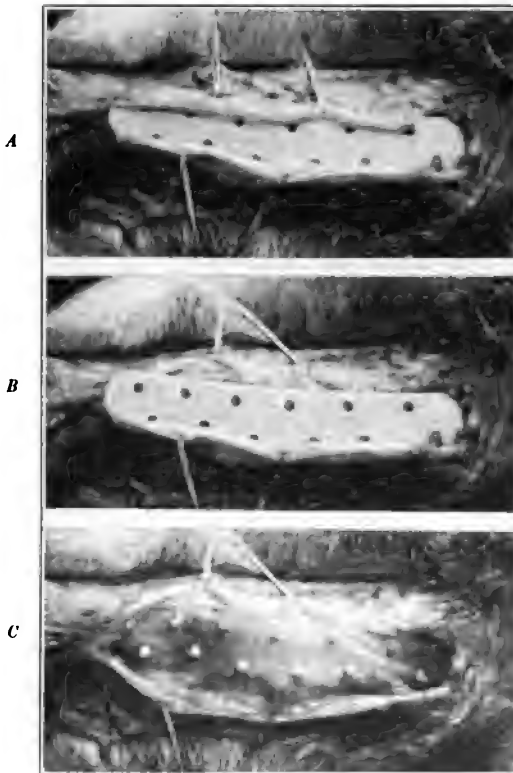


Fig. 269 (Dog B 684).—*A*, Tissue covering celluloid incised and retracted by sutures; note tissue extending down into perforations in the celluloid. *B*, margin of implant exposed by cutting tissue extending into perforations; note clean-cut margin of celluloid and tissue in perforations. *C*, surface left after removal of celluloid; note impression in bone at upper extremity where celluloid rested, and stumps of tissue which were in perforations.



in 1916, in an article on the use of celluloid in surgery, mentions the fact that it is of great value in cosmetic surgery of the nose.

I have not been able, however, to find any reference to the use of celluloid in plastic surgery of the nose in this country during the last ten years. In order to determine the advisability of its use in the correction of deformities of the nose, I inserted pieces of celluloid into the tissue over the nose in six dogs. The celluloid was obtained from a celluloid soap dish, and the pieces measured 6.3 by 1.2 cm., and varied in thickness from 2 to 2.5 mm. Several holes measuring 1.5 mm. in diameter were made in each piece. The celluloid was boiled for ten minutes for sterilization. Under ether anesthesia an incision was made down to the

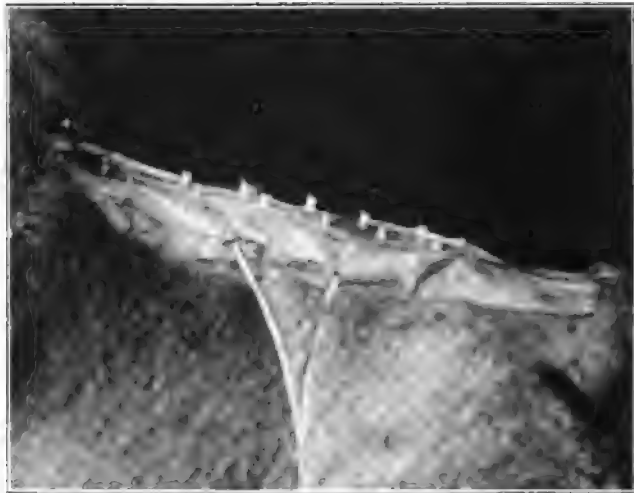


Fig. 270 (Dog B 684).—Note stumps of tissue which had extended completely through perforations in implant.

bone across the bridge of the dog's nose. With blunt dissecting scissors the tissues were elevated to make a pocket for the insertion of the piece of celluloid, which was placed in the pocket and the wound closed with silk sutures. In two of the six dogs the wounds became infected, and in the other four they healed nicely with practically no reaction, the celluloid acting as an ideal implant.

In the five cases in man the celluloid was obtained in a block about a foot square and three-eighths inch thick and sawed into pieces as needed by means of a "fret" saw. Several pieces, approximately what would be required, were shaped with a file before each operation, and then perforated with small holes about 1.5 mm. in diameter by means of a drill.

Pieces varying from 2 to 4 mm. in thickness have been used; they also are boiled ten minutes for sterilization.

The technic of inserting the implant is that in general use by men doing this work. It was recently described by the late Dr. E. H. Beckman for the use of cartilage from a rib. A curved incision extending down to the bone is made across the nose between the eyes where the bridge of a pair of glasses would rest. With small, blunt, curved eye scissors a pocket is made in the midline of the nose down to the tip. Care must be taken to keep the pocket in the midline and not to enter the nasal cavity.

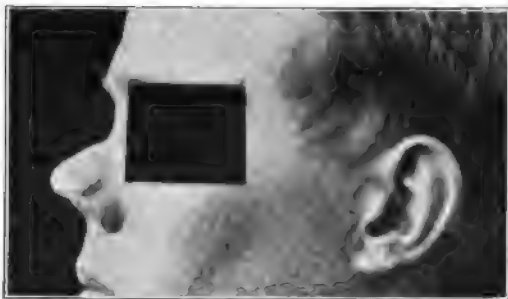


Fig. 271 (185775).—Before insertion of celluloid into tissue over the nose.

The piece of celluloid which will best correct the deformity is selected from those previously prepared, and if any trimming is needed, it is placed in hot water, when it may be cut with a knife as readily as cartilage; on cooling it becomes hard again. If it is necessary to curve the implant, placing it in hot water makes this possible, and it should

be held in the required position until it is cooled.

After the celluloid has been shaped, it is inserted down to the tip of the nose; the wound is closed with horsehair and sealed with tincture of benzoin compound. A

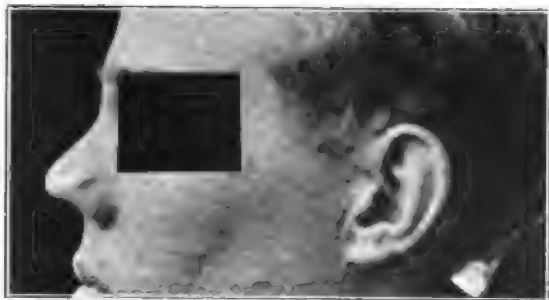


Fig. 272 (185775).—After insertion of celluloid into tissue over the nose.

thin copper splint is applied externally and held in place by adhesive plaster. In all the five cases the wounds healed primarily with practically no reaction. The implants have remained in position and have given no trouble; some of them have been in place for more than a year. I have not had an opportunity to use celluloid in a flap operation, but see no reason why it could not be thus used.

in 1916, in an article on the use of celluloid in surgery, the fact that it is of great value in cosmetic surgery of the nose.

I have not been able, however, to find any references to the use of celluloid in plastic surgery of the nose in this country. In order to determine the advisability of using celluloid for the correction of deformities of the nose, I inserted pieces of celluloid over the nose in six dogs. The celluloid was sterilized in a soap dish, and the pieces measured 6.3 by 2.5 mm. Several holes were made in each piece. The celluloid was sterilized by autoclave sterilization. Under ether anesthesia

from 2 to 4 mm. in thickness have been used. The celluloid is the CORRECTION of deformities of the nose.

For sterilization. Inserting the implant is that in general use by men. The implant is recently described by the late Dr. E. H. Berk. A curved incision extending from a rib. A curved incision extending



On palpation, the celluloid could be felt in position and could not be displaced; when the celluloid was exposed, it was found to occupy a definite pocket, but organization had not completely taken place through the perforations; the celluloid was easily removed; the tissue about the celluloid showed no inflammatory reaction; the implant was not altered in any way.

Fig. 270	2	6	219 days
bc			

On palpation, the celluloid could be felt in position and could not be displaced; when the celluloid was exposed, it was found to occupy a definite pocket, but organization had not completely taken place through the perforations; the celluloid was easily removed; the tissue about the celluloid showed no inflammatory reaction; the implant was not altered in any way.

CONCLUSIONS

It would seem from my experience with these cases that celluloid has several advantages as an implant in the correction of nasal deformities.

1. It eliminates the necessity of taking an autogenous transplant.
2. It causes practically no reaction when inserted in the tissues, and apparently is not affected by them.

may be readily trimmed or curved when placed in hot water.  
ains stiff even when trimmed quite thin.

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CELLULOID IN THE CORRECTION OF NASAL DEFORMITIES  
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## RESULTS OF EXPERIMENTS

EXPERIMENT	DOG	SERIES No.	TIME AFTER OPERATION	RESULTS
75-17	B-512	1	198 days	On palpation the celluloid could be felt in position and could not be displaced; when the celluloid was exposed it was found to occupy a definite pocket, but organization had not completely taken place through the perforations; the celluloid was easily removed; the tissue about the celluloid showed no inflammatory reaction; the implant was not altered in any way.
76-17	B-530	2	168 days	The celluloid was still in position, but was surrounded with pus; the material itself appeared to be the same as when embedded.
77-17	B-684	3	365 days	On palpation the celluloid could be felt in position, but could not be displaced; when the celluloid was exposed it was found to occupy a definite pocket, and its upper end was embedded in bone; the tissue over the celluloid was incised, and definite finger-like processes of tissue were found to extend through each perforation; the implant could not be removed until these were cut; the tissue about the celluloid showed no inflammatory reaction, and the implant was not altered in any way.
392-17	B-980	4	Unknown, at least 120 days	The site of the implant became infected, and the celluloid came out.
393-17	B-981	5	211 days	On palpation, the celluloid could be felt in position and could not be displaced; when the celluloid was exposed, it was found to occupy a definite pocket, but organization had not completely taken place through the perforations; the celluloid was easily removed; the tissue about the celluloid showed no inflammatory reaction; the implant was not altered in any way.
394-17	B-982	6	219 days	On palpation, the celluloid could be felt in position and could not be displaced; when the celluloid was exposed, it was found to occupy a definite pocket, but organization had not completely taken place through the perforations; the celluloid was easily removed; the tissue about the celluloid showed no inflammatory reaction; the implant was not altered in any way.

## CONCLUSIONS

It would seem from my experience with these cases that celluloid has several advantages as an implant in the correction of nasal deformities.

1. It eliminates the necessity of taking an autogenous transplant.
2. It causes practically no reaction when inserted in the tissues, and apparently is not affected by them.

3. It may be readily trimmed or curved when placed in hot water.
4. It remains stiff even when trimmed quite thin.

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# THE SURGICAL TREATMENT OF EPITHELIOMA OF THE LOWER LIP\*

W. E. SISTRUNK

When properly treated, epithelioma of the lower lip probably gives a higher percentage of cures than any other form of cancer. If all patients could be operated on in a radical way shortly after the appearance of the growth, there should be 95 per cent or more of cures.

There are certain factors which contribute to this high percentage of cures in epitheliomas situated at this point: (1) The majority of epitheliomas of the lip are, in the beginning, not very highly malignant. (2) The disfigurement and pain produced by the growth cause patients to seek comparatively early medical attention, consequently a large percentage of patients are operated on in the early stages of the disease. (3) The growth may be easily and thoroughly removed with little disfigurement. (4) All the lymphatic glands which drain the lower lip may be easily removed.

In spite of such favorable factors, however, many patients die each year from epithelioma of the lip. The deaths are largely attributable to the following causes: (1) Delay on the part of the patient in seeking medical aid. (2) Delay on the part of the examining physician to recognize the condition, and the tendency among many to use palliative measures or antispecific treatment first. (3) The tendency on the part of some surgeons to treat the condition by a local excision of the growth without removing the regional lymphatics. (4) The treatment of the growth by certain surgeons with radium, x-ray, or pastes without removing the glands. (5) Because many patients fall into the hands of the "quack" cancer specialists who do not perform radical operations.

The early diagnosis of epithelioma of the lip is not difficult, but it is extremely important. Any ulcer of the lower lip which persists for a few weeks should be looked on as being highly suspicious of cancer.

\* Paper prepared for the Mississippi State Medical Association, Jackson, Miss., May, 1918.

When such ulcers are surrounded by a slightly indurated area, the great majority of them prove to be epitheliomas. They are most commonly seen in males more than thirty-five years of age, but we have frequently found the condition in persons in the second decade of life; hence the age cannot be regarded as very important in considering the character of the growth. Practically the only other condition to be

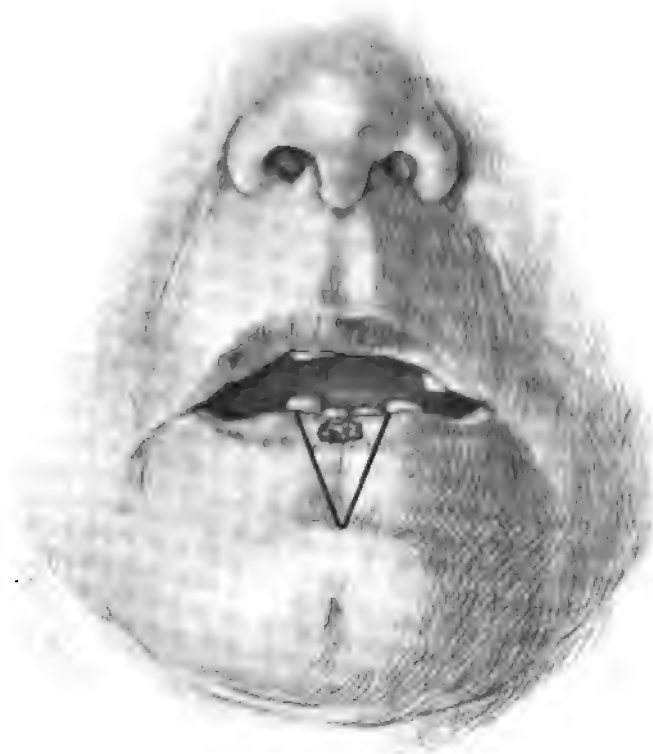


Fig. 273.—Ordinary V-incision, used in removing small growths from the lip.

taken into consideration in the diagnosis is syphilis. This, however, in our experience, has been very rarely found.

It is our custom to remove for diagnosis any chronic ulcer which is at all suspicious. If malignancy can be demonstrated in the tissue removed, a radical operation is performed immediately, or as soon afterward as possible. In all patients except those physically unfit, and very



old persons, we advise the removal of the growth and the glands draining the lip as soon as the diagnosis has been made. We believe that it is necessary to remove the glands from both submaxillary triangles, irrespective of the position of the growth on the lip. The lymphatic



Fig. 274.—Lip after the removal of the growth by the V-incision. Sutures placed and ready to tie.

anastomosis in this region is free and in case of the blocking of the lymphatics on either side, the lymph may drain through the lymphatics on the opposite side. We have frequently seen involved glands on the side of the neck opposite the growth, while no

glandular involvement could be demonstrated on the side containing the growth.

In small growths, when the diseased tissue can be removed by the ordinary V-incision, we usually do the gland dissection first. Immediately after this incision has been closed and while the patient is still under the anesthetic, the growth is removed from the lip (Figs. 273, 274, and 275). If the growth is extensive and it is necessary to remove a large portion of the lip, we also do the gland dissection first, then wait for five or six days and remove the growth

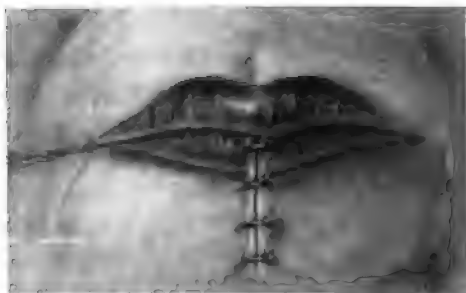


Fig. 275.—Lip after closure of the wound.

from the lip under local anesthesia, performing at the same time a plastic operation for the repair of the deformity produced (Figs. 276 and 277).

If no malignancy can be demonstrated in the glands that have been removed, dissection is limited to the removal of the glands and fascia from the submental regions and both submaxillary triangles. However, if

glandular involvement is found, all the glands draining the side of the neck on which the involvement is located are removed by what is ordinarily known as a block dissection. The technic employed in removing the submental and submaxillary glands as a prophylactic measure is as follows:

An incision is made parallel to the body of the lower jaw, at a point about midway between the upper portion of the thyroid cartilage and

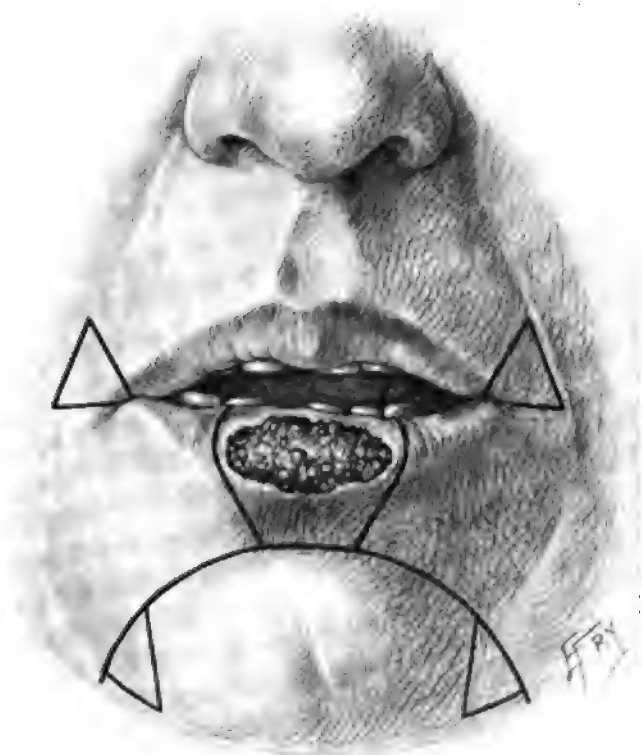


Fig. 276.—Incisions used in removing large growths from the lip and for the repair of the deformity produced. Quadrilateral segment of lip removed, followed immediately by a plastic repair.

the symphysis of the jaw, and extending from the inner border of the sternomastoid on one side to the same point on the opposite side (Fig. 278). The skin and platysma muscle are reflected upward as high as the jawbone, and all the glands and fascia lying between the anterior bellies of the digastric muscles (the submental group) are excised. The glands,

fascia, and fat, including the submaxillary salivary glands, are then removed from each submaxillary triangle. The lower jaw limits the dissection above, and the pulley and posterior belly of the digastric muscle are used as landmarks to limit the dissection below. Both submaxillary salivary glands are removed because they are surrounded by small lymphatics. The ducts of the submaxillary salivary glands are cut off just underneath the mylohyoid muscle, and the facial artery and vein are cut off at the level of the digastric muscle and again at the point where they cross the lower jaw-bone.

It is necessary to guard against the injury of: (1) The lingual branch of the fifth nerve, which runs underneath the mylohyoid muscle



Fig. 277.—Result after the lower lip has been largely remade by a plastic operation.

at a point just above the salivary duct; (2) the hypoglossal nerve, which comes underneath the digastric muscle near its pulley and then runs underneath the mylohyoid muscle just below the salivary duct, and (3) the inframandibular branch of the seventh nerve, which crosses over the facial vessels at a point about one finger's-breadth

below the jaw-bone. All these nerves are important and should be avoided: The lingual branch of the fifth nerve on each side supplies sensation to one-half of the tongue; each hypoglossal nerve supplies motion to one-half of the tongue, while the inframandibular branch of the seventh nerve, on each side, supplies motion to its half of the lower lip and angle of the mouth. The hyoglossus muscle forms the bottom of the submaxillary triangle, and all the fat down to this muscle is removed (Fig. 279).

The glands which have been removed are immediately examined under the microscope, and if involvement is found on either side, all of the glands on the side involved are removed as far down as the clavicle.

In such instances the primary incision is extended outward across the sternomastoid muscle and a second incision is then made at right angles to the first, beginning at the inner border of the sternomastoid above, and extending downward to a point near the juncture of the inner and middle thirds of the clavicle (Fig. 280). The skin and platysma are again reflected, and the sternomastoid muscle is cut off from its attachment to the clavicle. The glands and fascia from all the triangles on that side of the neck are then removed up to a point as high as the styloid



Fig. 278.—Incision used for removal of submaxillary and submental lymphatics.

process; the dissection extends down to the deep muscles of the neck, the glands and fascia lying along the carotid arteries and the internal jugular vein being removed. Care must be taken to avoid the phrenic nerve, the brachial plexus, the common and internal carotid arteries, and the hypoglossal, pneumogastric, and sympathetic nerves. The sensory branches of the cervical nerves are cut near the point where they emerge from the muscles. The omohyoid and sternomastoid muscles are removed and the spinal accessory nerve is sacrificed. The sacrifice of this nerve is followed, in the majority of instances, by paralysis of the trapezius muscle. We believe, however, that on account of the gravity

of the condition this deformity is permissible. The dissection can be done without the removal of the sternomastoid muscle and the spinal accessory nerve, but it requires much more time and probably is not so thorough an operation as when the muscle is removed. If the internal jugular vein is involved, it may be sacrificed on one side of the neck without fear of bad results. Injury to the common or internal carotid arteries necessitating the ligation of either of these vessels, in persons more than forty years of age, will be followed by a high mortality. If



Fig. 279.—Neck after the glands and fascia have been removed from each submaxillary triangle and from the submental region.

necessary, the external carotid may be ligated (Fig. 281). This operation, although a long one, is associated with a very low operative mortality.

The statistics, collected from the Mayo Clinic by Beckman, show about 90 per cent of cures in patients in whom a primary radical operation was done without involvement of the submaxillary glands. In a few of the cases, however, the growth on the lip was very extensive and, were it not for these, the percentage of results would have been considerably better. When all cases, both with and without glandular involvement, in which primary radical operation was done, were considered, there were 83.3 per cent of cures. There were 50 per cent of

cures in patients in whom the submaxillary glands were involved at the time of operation, and who were subjected to one of the complete block dissections. In the patients in whom the growth alone was removed, without the removal of the glands (on account of the physical condition or age of the patient), there were 73 per cent of cures. These statistics are almost identical with those of Bloodgood, and are probably a very true estimate of the percentage of cures obtained in epithelioma of the lower lip. In patients who have been operated on several times, with recurrences, or in patients with very extensive involvement of the lower group of glands, the percentage of cures is, of course, much lower. We have also found that when the growth, as frequently happens in the submaxillary triangles, becomes quite large, liquefies, and then breaks down, involving the surrounding tissues and skin, practically no cures are obtained. Operation is seldom advised in such cases.

Since its advent radium has been frequently used as a means of destroying the growth on the lip, while the glands have been left undisturbed. There is no doubt that such a procedure will destroy the growth; it is almost identical with the

methods in which the growth is removed with pastes or by local excisions. We know from experience that although there may be no local recurrence of the growth following the latter procedures, in about 30 per cent of the cases metastases later occur in the submaxillary or submental glands. We also know that when the submaxillary dissections are done as a prophylactic measure, although no malignancy can be demonstrated in the glands, about 95 per cent of cures are obtained. This shows that, although the pathologist is unable to demonstrate malignancy in the glands which have been removed, in about 25 to 30 per cent of these individual cancer cells are present, but cannot be recognized. If they are allowed to remain, they develop within a few years



Fig. 280.—Skin incision used in the block dissections.

and show as metastases in the submaxillary or submental glands. For this reason it seems wrong to use methods which are likely to be fol-



Fig. 281.—Block dissection which is done when the upper group of glands is found involved. Removal en masse of all glands and fascia from all the triangles, including the sternomastoid and omohyoid muscles.

lowed by such a high percentage of recurrences, when 95 per cent or more of the patients may be cured if the condition is operated on in its early stages by a method similar to the one outlined in this paper.

# THE USE OF HEAT AND RADIUM IN THE TREATMENT OF CANCER OF THE JAWS AND CHEEKS\*

G. B. NEW

Cancer of the jaws and cheeks is one of the most malignant forms of new growth. The type that is primary in the cheek is probably exceeded in its malignancy only by the melano-epithelioma. Little is known regarding the causation of such growths except that chronic irritation of some sort is believed to be an important factor, and, this being true, every snag of tooth or any other source of irritation should be eliminated from the mouth as a prophylactic measure. While tobacco may be a cause in some cases, it probably has not so much importance as is usually attributed to it. The man with cancer of the cheek who chews tobacco has, as a rule, carried the tobacco on the unaffected side of the mouth. Syphilis is undoubtedly a factor in the production of cancer of the tongue, but is of no demonstrable consequence in relation to cancer of the jaw and cheek. Papillary leukoplakia frequently develops into epithelioma, and it should be thoroughly treated with cautery and radium.

Fifty-seven cases of cancer of the jaws and cheeks were examined at the Mayo Clinic during 1917. Thirty-two of the patients were inoperable; 4 had glandular involvement, but operation was considered advisable and a block dissection was done in addition to the treatment of the local growth. Twenty-one had no glandular involvement and were treated with the cautery and radium. Data concerning these 21 patients form the basis of this paper. In most instances epitheliomas occurred in the fifth decade. There were two patients between thirty-one and forty years of age; 4 between forty-one and fifty; 12 between fifty-one and sixty, and 3 between sixty-one and seventy. Nineteen were men and two were women. The patients had first noticed the trouble from two weeks to four years before they came for examination, but it

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was difficult to determine the length of time the growth had been present or active. The tumor was located on the lower jaw in 2 cases, on the lower jaw and cheek in 7, on the upper jaw in 2, on the upper jaw and cheek in 7, and on the cheek in 3. Five of the 21 patients had been operated on before coming to the clinic. Seven of the epitheliomas were associated with, and apparently had originated in, a leukoplakia. In one case the tumor developed on a pathologic fracture of a bone cyst of the jaw.

#### TREATMENT

In reviewing the literature it is seen that the usual method employed in the treatment of cancer of the jaws and cheeks has been a complete or partial resection of the jaw with some type of plastic operation if the growth involved the cheek. Recently the cautery has been used in the treatment, but I have been unable to find any report in the literature of a group of cases treated in this manner. At the Mayo Clinic the cautery has been employed for several years in the treatment of such cancers, with a few exceptions, in preference to resection of the jaws. In many instances the radium has been used following the cautery.

During the year 1917 all the patients operated on were treated by the slow heat cautery with soldering irons, and, in addition, radium was used. While a report of recently treated cases of cancer must necessarily be only preliminary, nevertheless the results have been very encouraging, and I feel that we have obtained better immediate results than were obtained previously in the treatment of cases of this type.

In cases of cancer of the jaw or cheek without glandular involvement the decision as to whether or not they are surgical depends on individual judgment, but in any questionable case the patient should be given the chance an operation may afford, and everything possible should be done for him.

Before operation patients are advised that they must return for observation at least once a month during a period of six months or more following operation, so that they may have immediate care if there is any recurrence. When the seriousness of the condition and the necessity for coöperation are explained, it is usually not difficult to get patients to return at stated intervals.

#### TECHNIC

After the patient is anesthetized with ether, a mouth-gag is inserted opposite the affected side. The tongue is drawn to one side out of the

way, by the aid of a stomach clicker. The water-cooled speculum is inserted, and all the teeth in the area involved, or those that prevent good exposure of the growth, are removed. If it is possible, the entire growth is excised from the jaw or cheek with a knife cautery, and the base is cauterized with soldering irons. If this is not possible, the irons are inserted into the tumor. The water-cooled speculum prevents the burning of the lips or cheeks except in the area being treated, and it affords good exposure. A wooden tongue depressor holds the tongue out of the way and prevents it from being burned. The cautery should be used longer than seems really necessary—at least for from twenty to forty-five minutes. If the growth is in the upper jaw and involves the antrum, the soldering irons are carried up into the antrum and the entire growth is gradually burned away.

Soldering irons are found to be the most satisfactory type of cautery, as the heating element in the handle of the electric cautery usually interferes with a good view of the area that is being treated. If the irons are too hot, the surface cauterized becomes carbonized and prevents the penetration of the heat. A slow heat that gradually cooks the tumor is preferable.

Occasionally hemorrhage will occur during the first ten days or two weeks following the cauterization while the slough is clearing off, and if it is not readily controlled by packing, ligation of the external carotid with the lingual and facial branches is advisable.

About two weeks after the cauterization most of the slough will have cleared off, and radium may be applied directly into this open area. It is directed into the ulcerating area on lead applicators, using a 50 or 100 mg. tube within a silver tube, for from fifteen to twenty hours, without screening. If the growth has involved the cheek, radium is applied with screening externally over the cheek, thus cross-firing. If the growth has involved the antrum, the radium is placed in the antrum, packed there with petrolatum gauze, and left in place for the period of hours required by the particular type of lesion.

In from a month to six weeks after the operation, large pieces of sequestrum usually come away from the jaw. These pieces are sometimes one-fourteenth to three-eighths inch thick. In a month from the time the first radium treatment is completed further treatment is given and repeated as often as the condition indicates. If there is any recurrence noted, a second cauterization is done, and this is followed by radium.

Epithelioma of the jaw does not, as a rule, metastasize early, unless

there is considerable involvement of the cheek. In such a case the submental and submaxillary glands on the affected side should be removed.

### RESULTS

Of the 21 patients treated, 20 were traced; of these, 14 have been free of local recurrence for from six to eighteen months. One patient recatherized three months previously, thus far has no recurrence. One died of lymphatic leukemia six months after operation; there was no recurrence. Two of the 14 patients (one with epithelioma of the cheek and one with epithelioma of the upper jaw and cheek) have developed glands of the neck and have had block dissections. Thus 12 of the 20 patients have had no recurrence locally or in the glands for from six to eighteen months. One patient has a hopeless local recurrence. This patient was operated on before coming to the clinic. Two patients died of the cancer; one of these had been operated on before coming to the clinic; one consulted a plaster doctor, and his present condition cannot be learned from his letter. There was no operative mortality.

This group of cases shows that our immediate results in the treatment of epithelioma of the jaws and cheeks without glandular involvement, by the use of the cautery and radium, have been very encouraging. The end-results cannot be foreseen, but we believe that by the addition of radium to the treatment much more is being accomplished than formerly.

# THE VALUE OF RADIUM IN THE TREATMENT OF NEOPLASMS OF THE NOSE, THROAT, AND MOUTH\*

G. B. NEW

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It is now generally accepted, by those familiar with its use, that radium holds a distinctive place in the treatment of neoplasms. In no class of cases is it of greater value than in the types seen by the otolaryngologist. This is particularly encouraging because of the fact that the results following the surgical treatment of many of these neoplasms have not been satisfactory. The special value of radium in such cases is that it may be carried directly into the antrum, nasopharynx, or larynx, and thus come in direct contact with the neoplasm.

Radium has a specific or alterative action on certain tissues, such as basal-cell epithelioma, sarcoma, angioma, etc., causing the tumors gradually to shrink up and disappear. Its action on other types of tissue, for example, the squamous cell epithelioma, is destructive. The more rapidly growing tumors, such as lymphosarcomas, are made to disappear much more readily by the use of radium than are the slow-growing tumors, such as mixed tumors of the parotid or slow-growing fibromas of the nose.

## METHODS OF APPLICATION

The radium is applied in the form of a plaque or disc, over the surface of which it is spread out and held in place by a varnish; or it is applied in a glass tube inside of a silver tube about one-sixteenth by one-half of an inch in size. The disc form of application is used with little or no screening, in superficial lesions, or it is screened and applied to penetrate, as in the treatment of glands of the neck. The tubes are used with screening in applications over the tumor, or they are inserted directly into the tumor. The size of the tube usually employed con-

\* Presented before the Ontario Medical Assn., Hamilton, Ont., May, 1918. Reprinted from the Canadian Med. Week, 1918.

are exclusive of the cases of basal lesions of the nose, face, etc. While it is too soon to report end results in this group I shall, in a general way, outline the results to the present time:

<b>1. Nose (intranasal)</b>		<b>5. Larynx</b>	
Epithelioma	9	Epithelioma	21
Papilloma	3	Multiple papilloma	13
Myxoma	3	Angioma	2
Sarcoma	1	Amyloid	3
	—	Lupus (pharynx and larynx)	2
Total	16	Total	41
<b>2. Nasopharynx</b>		<b>6. Jaws and cheeks (intra-oral)</b>	
Epithelioma	5	Epithelioma	47
Myxoma	3	Sarcoma	3
Fibromyxoma	1	Lymphangioma	2
Fibrosarcoma	1	Adamantinoma	3
Lymphosarcoma	3		—
Malignant tumor	1	Total	55
Total	14		
<b>3. Antrum</b>		<b>7. Palate</b>	
Epithelioma	9	Epithelioma	7
Sarcoma	4		
Myxoma	1	<b>8. Tongue</b>	
Fibroma	1	Epithelioma	13
Total	15	Lymphangioma and angioma	10
		Lymphosarcoma	1
		Total	24
<b>4. Pharynx and tonsil</b>		<b>9. Upper lip</b>	
Epithelioma	6	Angioma	11
Sarcoma	4	Basal cell epithelioma	8
	—	Lymphedema	8
Total	10	Total	27
		<b>10. Lower lip</b>	
		Angioma	2

*Tumors of the nose.*—Angiomas of the external nose are readily taken care of by radium, and the results are far superior to those obtained with the use of hot water injection or CO<sub>2</sub> (carbon dioxid) snow. In the cavernous type the radium is inserted directly into the tumor. The basal cell epithelioma of the nose formerly was excised with a cautery, especially if the cartilage was involved. Later, if the condition was cured, a plastic operation was necessary to close the opening of the nose. Such growths are now cleared up with radium with the smallest amount of deformity, if any.

*Intranasal and nasopharyngeal tumors.*—Sarcoma, myxoma, and fibroma are best treated with radium. The operative treatment of such tumors usually involves considerable risk, because of the liability to hemorrhage, and in most cases the tumor recurs. By the use of radium the patient is usually markedly benefited, receiving months or years of

relief, if indeed the condition is not entirely cleared up. In the treatment of such tumors, other than the fibroma or fibrosarcoma, it is best to apply the radium to the cervical regions also, in order to prevent glandular involvement.

Operative measures in the treatment of epithelioma of the nose are usually of little value. Radium frequently clears up the ulceration and discharge and scars down the growth, giving the patient much relief, and sometimes accomplishing more than this. Myxomas of the nostril, which are not associated with a sinus infection and which always recur after removal surgically, are caused to disappear by the use of radium.

*Tumors of the antrum.*—

In cases of malignancy of the antrum, unless of the type of fibroma or fibrosarcoma that shells out readily, the condition is treated almost exclusively by making an opening into the antrum above the alveolar process by means of a soldering iron and inserting radium.

In one group of cases, especially if the cheek is involved, treatment by resection of the upper jaw is not satisfactory. The method

of cooking the tumor by means of soldering irons and slow heat for from one-half to three-fourths of an hour, followed by radium in the cavity, is to be preferred and gives much better results, notably in cases of sarcoma.

*Tumors of the pharynx and tonsil.*—Probably the most spectacular results are obtained in the treatment of a lymphosarcoma of the pharynx. A huge mass filling the pharynx will melt away, and in three or four days disappear without leaving a trace. In such cases, however, enlarged



Fig. 284 (225487).—Extensive lymphosarcoma of right nasopharynx and pharynx, bulging the soft palate.

cervical glands frequently develop, and while these may be cleared up, the patients may die of chest metastasis, although they have received months or years of relief and comfort. Such conditions are hopeless surgically, and radium will accomplish a great deal.

With all the measures at our disposal, epitheliomas of the tonsil are very difficult to clear up, but we have one patient who has been free from recurrence for nearly two years following an extensive recurrence after excision and cautery. Other patients have been markedly relieved and improved, and we feel that the possibility of improvement and help

warrants the use of large doses of radium, preferably after removal of the growth. If there is a good possibility of improvement in the local growth, a block dissection should be done and this followed by radium over the neck. Lupus of the pharynx is readily cleared up with radium; this seems to be the most satisfactory way of treating it.

*Tumors of the larynx.*—

An extensive squamous-cell epithelioma of the larynx is usually considered a hopeless problem, since surgery offers very little in the way of relief. We have treated such cases by doing a tra-



Fig. 285 (225487).—Same as Fig. 284, five days after insertion of radium.

cheotomy, and after cocaineization, dropping the radium directly into the larynx. The radium is held in place for from one to one and one-half hours at a time. While all patients are not benefited, very encouraging results and remarkable relief have been obtained. One man had an extensive carcinoma of the larynx obstructing the glottis so that it was necessary to do a tracheotomy; he was swallowing fluids only. In two months' time he had gained forty-eight pounds and could eat anything. He had a cork in the tracheotomy tube. The growth did not recur locally, but the patient died of chest metastases about fourteen

months later. However, the treatment gave him a year of comfort. The local tumor does not always completely disappear, as in the foregoing case, but the patients that do improve make one feel that everything possible should be done to give them the benefit of radium.

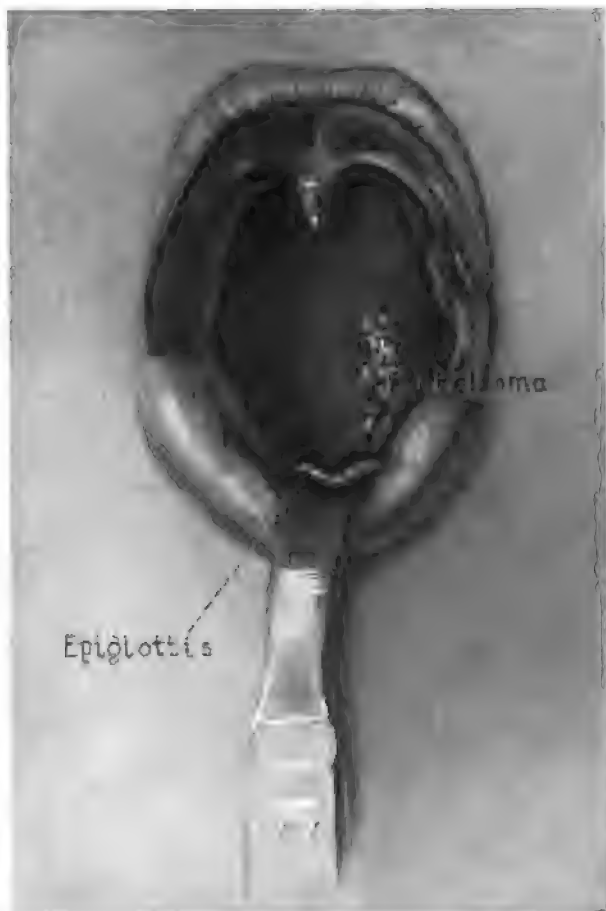


Fig. 286.—Epithelioma of the left posterior pharyngeal wall.

Lupus of the larynx is treated by dropping the radium down into it after cocainizing. The results are very good.

One case of angioma of the larynx, causing dyspnea in a child, which would have been very difficult to benefit in any other way, was entirely cleared up by the external application of radium.



The treatment of multiple papilloma of the larynx in children has been improved wonderfully by the addition of radium. The patient is suspended with the Lynch suspension apparatus, the papillomas are cleared out, and while thus suspended the radium is placed in the larynx. We have treated two cases of multiple papilloma of the larynx in children without tracheotomy, the only treatment being radium on the outside of the neck. The tumors cleared up entirely and have not recurred.

*Lips.*—Ulcer of the lip or epithelioma of the lip should not be treated

with radium. Every suspicious lesion of the lip should be excised for diagnosis, and if it is found malignant the submaxillary and submental glands should be removed. Many such lesions may readily be cleared up with radium, but it cannot be determined whether or not the lesion is malignant without a microscopic examination. Many patients come with metastasis in the neck when an epithelioma of the lip has been removed with radium or some other means, and no glandular dissection done.



Fig. 287.—Scar of epithelioma of left posterior pharyngeal wall after treatment with radium.

*Tumors of the jaw and cheek.*—In the treatment of malignancy of the jaw

and cheek the growth, if surgical, is first thoroughly cauterized by slow heat cautery by means of a soldering iron. In about two weeks radium is applied directly into the raw area. The radium is applied again in from three to four weeks, and as often as necessary later. The addition of radium to the treatment has made our immediate results much better than they have ever been before. Twenty-one cases of cancer of the jaws and cheeks were treated during the year 1917; 20 of the number have been traced; 14 of these have had no local recur-

rence. In 2 of the 14 cases glands of the neck have developed, and block dissections have been done. In one case of primary squamous-cell epithelioma of the cheek almost perforating, the tumor cleared up entirely, and there has been no recurrence for more than a year. This, of course, is an unusual result, but it is a stimulant to give the patient this chance of help in many inoperable cases.

Leukoplakia of the mucous membranes of the mouth is treated with radium, and the condition cleared up.

*Tumors of the tongue.*—Cases of lymphangioma and angioma of the tongue are very difficult to deal with surgically and, as a rule, very little



Fig. 288 (163203).—Extensive active epithelioma of the bridge of the nose and both inner canthi. Fixed to the bone before radium treatment.



Fig. 289.—Same as Fig. 288, after radium treatment.

is accomplished. Radium is a specific for these conditions, and very large tongues will become reduced almost to normal in a few weeks or months. Radium is either inserted directly into the tongue, or screened and applied over the tongue.

Radium is employed in epithelioma of the tongue, occasionally alone, if the condition is inoperable or if the patient's general condition will not permit operation. It is more frequently used post-operatively after excision of half the tongue and block dissection. The radium decreases the discharge, scars down the lesion, and makes the patient much more comfortable.

I have not seen in the literature reports of the use of radium in thrush, but in our experience its repeated application has eliminated this very persistent trouble.

### RESULTS

The immediate results of the treatment of the neoplasms of the nose, throat, and mouth with radium are, as a whole, very encouraging. Many patients previously operated on with a recurrence following are now treated with radium and the neoplasm disappears, giving months or years of relief, with no surgical mortality. The patients are made much more comfortable than they would be with an operation. The number of patients that will be permanently cured of a true malignancy with radium is probably very small relatively, but the number of inoperable cases that are markedly relieved and receive months or years of comfort is quite large. We do not, however, recommend the treatment by radium of any neoplasm that is surgical. In such cases the patient should have the benefit of both surgery and radium. The use of radium has changed entirely the prognosis in neoplasms of the nose, throat, and mouth.

## ANKYLOSIS OF THE JAW\*

M. S. HENDERSON AND G. B. NEW

The different methods employed in the treatment of ankylosis of the jaw, and the length of time elapsing before patients apply for treatment after almost a complete fixation, would seem to indicate that the good results obtained by arthroplasty of the temporomaxillary joint are not generally known.

During the last eight years at the Mayo Clinic 23 cases of ankylosis of the lower jaw have been treated—14 within the last three years. Depending on the location of the fixation, such cases divide themselves into three groups: (1) The articular type, in which the joint alone is involved; (2) the extra-articular type, in which the fixation is extra-articular, such as scarring in the muscles of the cheek or temporal region; and (3) the articular-extra-articular type, in which the cause of the ankylosis is both within and without the joint. Of the 23 cases, 15 were articular, 5 extra-articular, and 3 articular-extra-articular. Twenty-two resections of the condyle were done—19 in the articular cases and 3 in the articular-extra-articular cases.

### ETIOLOGY

The etiology of the articular cases of ankylosis is either traumatism or infection extending into the joint by direct extension or by the bloodstream. Blair, in reviewing the literature of the articular variety of ankylosis, states that 50 per cent of the cases are due to trauma on the chin. In our group of cases only 3 (20 per cent) were due to this cause. Murphy states that most cases of ankylosis of the jaw are due to extension from middle-ear infection directly into the glenoid cavity or over the base of the zygoma into the joint. In one only of our cases was an ear infection the probable cause of the ankylosis. A child developed a running ear after scarlet fever, and this was followed by ankylosis of the

\* Presented for publication February 1, 1918. Reprinted from *Surg., Gynec., and Obst.*, 1918, xxvii, 451-458.

jaw on the same side. Table 1 shows the various causes to which the condition is attributable in our group of cases:

TABLE 1.—TWENTY-THREE CASES

<i>Articular</i> .....	15	<i>Extra-articular</i> .....	5
Trauma of the chin.....	3	Infection of cheek from teeth.....	1
Recurring dislocation of jaw.....	1	Slough of cheek from "salivation".....	1
Osteomyelitis of jaw.....	1	Abscess of temporal region, cause unknown.....	2
Scarlet fever.....	1	Temporal abscess from wisdom tooth.....	1
Measles.....	1		
Abscess of cheek over articulation.....	1	<i>Articular-extra-articular</i> .....	3
Arthritis.....	1	Three unsuccessful tonsillectomies and quinsy.....	1
Not stated.....	1	Abscess outside of ramus from teeth.....	1
Fever.....	1	Baseball injury over joint and secondary abscesses.....	1
Typhoid.....	2		
Tonsillitis.....	1		
Diphtheria.....	1		

It should be remembered that on account of the early age at which this condition often occurs it is sometimes difficult to get a clear history of the cause of the trouble. In the extra-articular cases some fixation in the muscles or structures about the joint, such as scarring of the muscles of the neck or temporal region secondary to abscessed teeth, tonsils, etc., caused the ankylosis. In one case the fixation was inside the lower jaw owing to the scarring following quinsy and attempted tonsillectomy.

In most cases the age of the patients at the time of the occurrence of the articular type of ankylosis of the jaw was under ten years.

TABLE 2

AGE	CASES	AGE	CASES
1-10 years.....	9	21-30 years.....	2
11-20 years.....	3	53 years.....	1

The ages of the patients at the time of the occurrence of the extra-articular and articular-extra-articular types are shown in Table 3.

TABLE 3

AGE	CASES	AGE	CASES
1-10 years.....	2	31-40 years.....	1
11-20 years.....	2	41-50 years.....	1
21-30 years.....	2		

In the latter group the condition seemed to be about equally divided over the first five decades. In the articular group 9 of the 15 cases occurred in patients under ten years of age. Taking these two groups as a basis, it is seen that nearly 50 per cent of all cases of ankylosis of the lower jaw occurs in the first decade. As may be noted in Table 4, most

of the patients do not come for operation until they are between twenty-one and thirty years of age.

TABLE 4

AGE	CASES	AGE	CASES
1-10 years.....	4	31-40 years.....	1
11-20 years.....	6	41-50 years.....	1
21-30 years.....	10	51-60 years.....	1

### PATHOLOGY

The growth of the ramus of the jaw is largely dependent on the epiphysis of the condyle, and any fixation of this with consequent loss of function interferes with the development of the jaw on the side affected. The underdevelopment and shortening of the affected side cause the typical deformity seen in such cases. The center of ossification of the condyle does not unite with the ramus until the fifteenth year. Injury to or fixation of the condyle before the jaw is fully formed would cause the lack of development of that side. In the fibrous type of ankylosis fibrous adhesions occur in the joint, while in the bony type the entire joint is sometimes obliterated and the condyle and zygoma form one mass of bone with no definite landmarks. In the extra-articular group the scarring prevents the normal elasticity of the muscles, usually the temporal, masseter, or pterygoids, and thus limits the movements of the jaw.

### PHYSICAL FINDINGS AND DIAGNOSIS

The case of unilateral ankylosis of the lower jaw, if the condition has occurred before the jaws are fully formed, presents a typical picture (Figs. 290 and 291). The chin is markedly retracted and is displaced toward the affected side, which appears full and rounded while the normal side is flattened. The midline of the lower jaw is displaced to the affected side, and when the patient separates the teeth, if there is any movement of the jaw, the midline moves to this side. Radiograms of the ascending rami show a shortening of the ramus of the affected side (Fig. 292). If the ankylosis is bilateral or has occurred after the complete development of the jaws, then the findings are altered. In the latter group of cases it is sometimes impossible to differentiate the side involved from the physical findings alone. A differentiation between a bony and fibrous ankylosis is usually readily made as the bony type allows of practically no movement of the jaw. The amount of movement that can be obtained in unilateral bony ankylosis at times is surprising. A definite diagnosis

of the side affected can be made only if the condition has occurred early in life, when there is typical deformity, or when the patient's history can be relied on to show the side affected if there is no deformity.

In older patients with fibrous ankylosis a very slight movement of the jaw will sometimes serve to establish the affected side. Radiograms of the joint itself are usually of little value, as the physical findings are sufficient to determine whether the ankylosis is fibrous or bony, although occasionally a radiogram is obtained from which a diagnosis of bony ankylosis could be made from the plate alone. Nine of the 15 cases of articular ankylosis in our group were bony and 6 fibrous.



Fig. 290.—Bony ankylosis of right lower jaw. Note retrusion and displacement of the chin to the right and the flattening of the left side of the face.

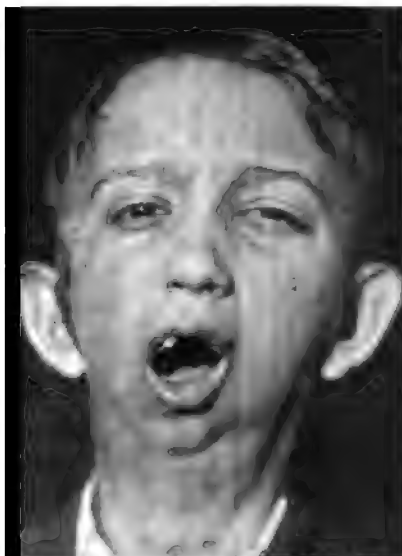


Fig. 291.—Same as Fig. 290 after arthroplasty.

Little was noted in the literature of the clinical differentiation between the articular and extra-articular types of ankylosis, though usually such differentiation is not difficult. Two of our patients (adult men) in whom there was no deformity serve to illustrate this point. The side affected was easily determined by the divergence of the jaw to the side affected when the teeth were separated, the condyle on that side having very little movement while the opposite side moved quite readily. In one of the patients the ankylosis came on after attempted tonsillectomy and recurring quinsy, and in the other following a recurring

abscess of the cheek outside the ascending ramus. In both instances it was impossible, until the joint was explored and resected, to deter-



Fig. 202.—Patient, twenty-five years of age. Comparative shortening of right ascending ramus. Ankylosis of the right lower jaw which came on following typhoid fever when patient was eleven years of age.

mine that the ankylosis was the result of two factors, namely, the articular and the extra-articular. The question of the coronoid process being the cause of any fixation was readily ruled out in these two



cases. There was sufficient scarring in one case inside the ramus, and in the other outside the ramus, to prevent the teeth from separating for more than one inch.



Fig. 293.—Note the superficial temporal artery, internal maxillary artery, facial nerve, and the location of the incision.

#### TREATMENT

For many years excision has been the surgical procedure for ankylosis of the temporomaxillary joint. In the main the results have been satisfactory, but the occasional failure has spurred surgeons to modify the technic. The impetus given by the late J. B. Murphy to the use of a flap of autogenous fat or fascia in arthroplasties has led the majority of writers to recommend the placing of such tissue between the denuded

bone ends when operating on the jaw for ankylosis. Baer has advised the use of chromicized pig's bladder and reports good results.

Excision of the joint is, however, the basic principle of each method advised. Any operation which is designed to give motion to a previously ankylosed joint, or one in which the motion is sufficiently restricted to prevent the function of the joint, should be called an arthroplasty, whether the technic of such operation demands merely the removal of enough bone to allow motion, or whether it includes as a step the inter-

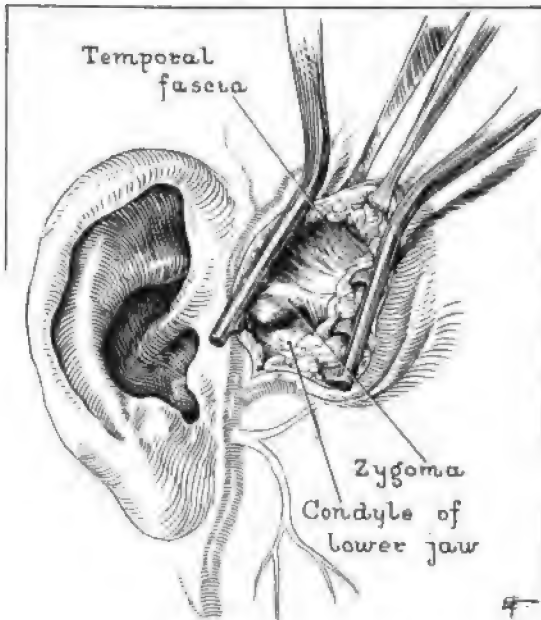


Fig. 204.—Exposure of the zygoma and condyle. The retractor holds the soft tissues and facial nerve downward and forward in the flap.

position of fat, fascia, or some foreign substance between the bony surfaces to prevent a subsequent ankylosis.

The operation herein described is an arthroplasty, because it has as its object the establishment of sufficient motion to permit function of the part affected. The facial nerve and the internal maxillary and superficial temporal arteries are the structures the surgeon must bear in mind and familiarize himself with before undertaking the operation. The facial nerve, after it leaves the stylomastoid foramen, passes downward, outward, and forward through the parotid gland and divides just posterior to the ramus of the mandible into the terminal branches; the temporo-

facial and the cervicofacial. It is to the former branches that damage is most likely to be done during the operation under discussion. These branches run upward and forward from just below and in front of the external auditory meatus as they arise in the parotid gland from the main nerve. The external carotid artery branches into the superficial temporal artery and is continued on as the internal maxillary. The superficial temporal branch runs straight up to the temporal region, being superficially placed close to, and in front of, the external auditory meatus. The internal maxillary artery is deeply situated, and on its way



Fig. 295.—The zygoma over the joint is removed, giving a better exposure for the removal of the condyle. Note small bridge of zygoma remaining.

to the pterygoid fossa of the sphenoid bone courses close to the inner side of the neck of the ramus of the mandible (Fig. 293). The artery is not especially liable to injury and is well out of the way if, during the operation, all work is kept close to the bone. Some little bleeding may occur from the articular branches which are given off, but packing with a hot salt sponge for a minute or two controls this if it proves to be annoying. If the bleeding is persistent and considerable in amount, it means that damage has been done either to the superficial temporal artery, which lies behind, or to the internal maxillary itself.

Taking these anatomic structures into consideration, it will be seen that there is a triangular area with the base upward lying over the temporomaxillary joint which is practically devoid of important anatomic structures, and permits a ready and safe approach to the joint. To carry out the "safety first" idea to its completion, as regards the facial nerve, the approach should be consistently made from above, and in order to do this the lower portion of the zygoma over the joint must be sacrificed, but a bridge is left so that no deformity will result. This

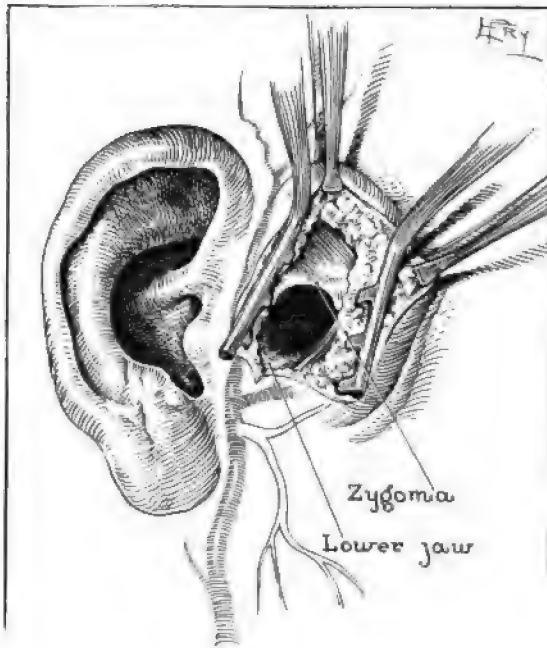


Fig. 296.—The condyle removed, exposing the space between the upper end of the ascending ramus and skull.

approach is particularly of value in a case with marked deformity in which the joint is very low, and in order to expose it directly it would be necessary to injure the facial nerve. Hartley has described an operation very similar to that used by us except that he begins the incision behind and turns the ear down, thus necessarily dividing the superficial temporal artery, a matter of very little consequence, however.

The incision used by us is curved and about two inches long. Its anterior and upper portion runs one-half inch above and parallel to the zygoma. The posterior arm extends downward just in front of the ear

to about the level of the floor of the external auditory canal. This skin-flap is partially dissected free in order to expose the zygoma. If



Fig. 299.—Same as Fig. 297 after operation.



Fig. 298.—Note typical retraction of the chin. Same case as Fig. 297. Also note scar from operation of arthroplasty.



Fig. 297.—Fibrous ankylosis of the right lower jaw. Note displacement of the midline of the lower jaw to the right.

necessary, the superficial temporal artery may be divided. An incision parallel to the zygoma and directly over it is made and the temporal fascia is retracted downward, exposing the zygoma and the joint region. The entire flap is then turned downward and forward, carrying with it and holding out of the way of injury the temporofacial branch of the facial nerve. The safest form of retraction is by the use of a self-retaining mastoid retractor placed obliquely in the wound (Fig. 294). If the retraction is left to an unskilled assistant, he may, in his zeal for exposure, use too much force and a temporary facial paralysis will occur, the result of stretching. The next step consists in the removal of the part of the zygoma directly over the joint area, care being taken not to injure the external auditory canal and to leave a small bridge of the zygoma to maintain facial contour. This exposes the condyle and it can be removed with a chisel gouge (Fig. 295). The bone to be taken out should be carefully removed by chiseling off small pieces. If rongeur forceps are used and big bits taken, and the bone is twisted out,

the internal maxillary artery may be injured. It not infrequently happens that when there is a bony ankylosis the ramus and even the coronoid process is involved in the mass. A large quantity of bone must then be

removed and a space at least one-half inch in width must be left between the neck of the ramus and what formerly was the glenoid fossa (Fig. 296). If the coronoid process is involved, a sufficient amount of it must be removed to permit free motion. This can be done by working forward through the same exposure. No fascia, fat, membrane, or foreign material of any kind is placed between the end of the mandible and the temporal bone. When the bone is removed and motion secured, the wound is closed.

If, after the completion of the arthroplasty, sufficient motion has not been obtained, in a case in which there is no facial deformity and in which it has not been possible definitely to determine the side chiefly affected, the surgeon is forced to conclude that the other side is at fault, in which case the second side should be operated on later. On the other hand, occasionally after the removal of bone the amount of motion obtained has been disappointing, though there has been

no question but that the side operated on was the affected side. In such a case the trouble is in the muscles and peri-articular structures. Too vigorous attempts to open the jaw widely with the mouth-gag or the threaded block of wood are to be condemned, for the teeth are often broken needlessly. By patiently forcing the mouth open each day with a mouth spreader, motion will steadily improve. The patient himself uses this spreader. He is encouraged to chew gum and thoroughly to chew meat, preferably tough meat, at his meals (Figs. 297, 298, 299, and 300).



Fig. 300.—Note the threaded top used to separate the teeth after operation.

### RESULTS

Nearly all the 15 patients on whom arthroplasties were performed have done well. During the last three years in all the cases, which

include ten articular and two articular-extra-articular, from one inch to one and three-quarter inches separation between the teeth with good free movement has been obtained. In some of the earlier cases the results were not quite so good. With improvement in technic the results have been better. As applied to our entire group of cases the operation described has been uniformly satisfactory.

In the articular-extra-articular cases equally satisfactory results have been obtained, although the scarring in the muscles has prevented the wide separation that was obtained in the others. In all of these cases, however, there is at least one inch separation between the teeth.

The extra-articular cases present a different problem; they are not benefited by the operation under discussion and our best results have been obtained by forcible stretching under ether.

### CONCLUSIONS

We believe that the essential points in this method of treating articular ankylosis are:

1. Removing sufficient bone to make a space one-half inch between the skull and the ramus and thus obtaining a stable functioning joint.
2. An incision that gives good exposure to the joint and does not injure the facial nerve.
3. Approaching the joint from above by removing part of the zygoma.

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# PARTIALLY AUTOLYZED PNEUMOCOCCI IN THE TREATMENT OF LOBAR PNEUMONIA

## RESULTS IN 200 CASES\*

E. C. ROSENOW

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The curative power of antipneumococcus serum in lobar pneumonia due to Type I pneumococcus appears to be established.<sup>1</sup> According to Cole,<sup>2</sup> of every 100 patients with lobar pneumonia admitted to hospitals, the infection in about 35 cases is due to Type I pneumococcus, 10 dying if untreated. The remaining 65 cases are due to the other types of pneumococci, and in these, 20 deaths occur. Hence about two-thirds of the cases of lobar pneumonia and two-thirds of the deaths from the disease are due to pneumococci, for which there is at present no specific serum treatment.

It has been established that heat-killed virulent pneumococci stimulate the formation of antibodies<sup>3</sup> and tend to protect animals against pneumococcus infections. Active immunization with heat-killed pneumococci<sup>3</sup> and various derivatives of pneumococcus cultures<sup>3</sup> have been used in small series of cases of lobar pneumonia, in some instances with seeming benefit.

There are numerous physicians with a keen perception of lobar pneumonia who feel that active immunization with pneumococcus vaccine, when the vaccine is given early in large doses, is of benefit. The disadvantage of heat-killed pneumococci in which the toxic material has not been removed is considered to be due to the primary negative phase which follows their injection. In connection with studies on the mechanism of pneumococcus infections and the nature of the toxic substance obtainable from pneumococci, attempts were made to separate, in part, the toxic from the antigenic fractions. It was found that the protective power against pneumococcus infections was greater with partially autolyzed pneumococci from which a large part of the toxic substance had disappeared than with heat-killed pneumococci.<sup>4</sup>

\* Reprinted from Jour. Am. Med. Assn., 1918, lxx, 759-763.



On the basis of these experiments, a method of active immunization with partially autolyzed pneumococci was developed, and its apparent value in the treatment of lobar pneumonia has been emphasized from time to time.<sup>5</sup> The mortality rate in 146 cases treated by Hektoen and myself in the Cook County Hospital, Chicago, during three consecutive winters, was 23 per cent, while in untreated alternate control cases it was 38 per cent. This was accomplished notwithstanding the fact that the average time of the first injection was four and one-half days after onset, and that the cases treated were of the most unfavorable type, a majority of the patients being addicted to the excessive use of alcohol. During 1914 and 1915 this pneumococcus antigen was sent on the request of physicians in different parts of the country, and reports of cases were rendered.

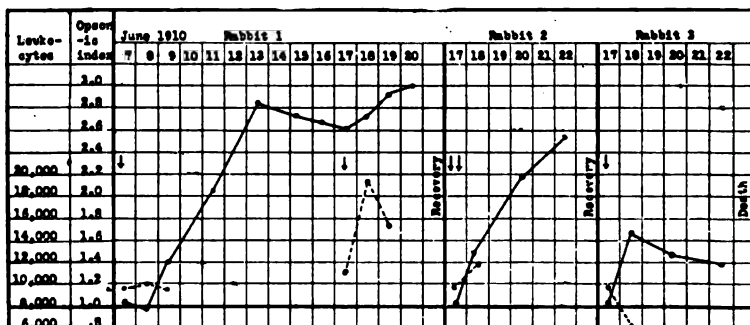


Chart 1.—Immunizing power of autolyzed pneumococci against pneumococcus infection in rabbits: Continuous line, opsonic index for pneumococci; dotted line, leukocytes; arrows, time of injections.

The stimulus for reporting our results at the present time is the prevalence of pneumonia among the troops in the concentration camps. I wish also to record a few of the experiments which led to the use of this antigen and to describe the method of its preparation and administration as now practised.

#### EXPERIMENTS ON THE IMMUNIZING POWER OF VARIOUS AUTOLYZED FRACTIONS OF PNEUMOCOCCI

In Chart 1 are shown the opsonic and leukocyte curves and the protective action of autolyzed pneumococci against pneumococcus infection in rabbits.

Rabbit 1 was injected subcutaneously with 3 billion autolyzed pneumococci, and ten days later with a culture of a moderately virulent

pneumococcus. Rabbit 2 was injected simultaneously with the same sized dose of autolyzed pneumococci and culture, and Rabbit 3 was injected with the culture only. Autolysis had been continued for ninety-six hours, and the clear extract had lost most of its toxic properties. Rabbits 1 and 2 recovered coincident with a high opsonic index for pneumococci and a sustained leukocyte curve. Rabbit 3 died coincident with first a slight rise in opsonins, and then a drop in opsonins and leukocytes. The results obtained simulated what occurs in non-fatal and fatal cases of lobar pneumonia.<sup>8</sup> By properly balancing the dose of antigen and the living culture, similar results were obtained in a series of experiments on rabbits and guinea-pigs. It was found that if the dose of antigen was too large or autolysis was not carried far enough, death might occur earlier in the animals receiving antigen and culture than in

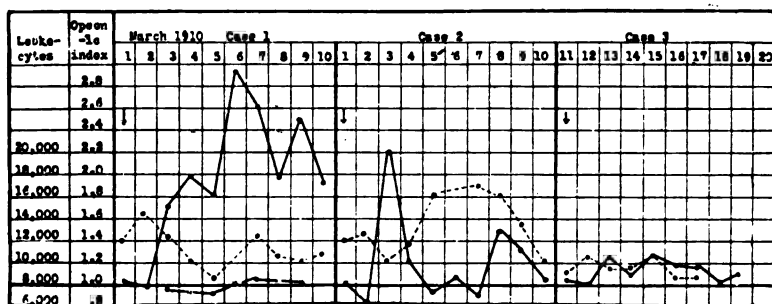


Chart 2.—Opsonic and leukocyte curves in three persons injected subcutaneously with various autolyzed fractions of pneumococci: Continuous line, opsonic index for pneumococci; broken line, opsonic index for streptococci; dotted line, leukocytes; arrows, time of injections.

those injected with the culture only. Protection was afforded in some instances even after intraperitoneal injection of the cultures.

Patient 1 (Chart 2) was injected with 5 billion partially autolyzed pneumococci, Patient 2 was injected with the corresponding clear extract, and Patient 3 with the extract after it had been treated with leukocytes. In the first case there were early rise in and a sustained opsonic index for pneumococci, no change in the opsonic index for hemolytic streptococci, little change in the number of leukocytes, no fever, and only slight local reaction. In the second case there were primary drop and then a transient rise in opsonic index for pneumococci, a slight increase in the number of leukocytes, a rise in temperature, and a moderate local reaction. In the third case there were no changes in opsonic index, leukocyte count, or temperature, and no local reaction.

From these and other similar experiments it was concluded that partially autolyzed pneumococci had greater and more sustained antigenic powers than the more toxic extract, and that leukocytes had the power to destroy completely the antigenic power of the extract. The experiments on animals showed that the doses of antigen and culture needed to be balanced quite accurately in order to protect against the infection.

In Chart 3 are given the opsonic index and temperature curves of three persons injected with, respectively, 20, 40, and 60 billion autolyzed pneumococci. According to this experiment, the first dose (20 billion) was regarded as the most favorable, and this was the dose used in the treatment of patients during the winter of 1911.

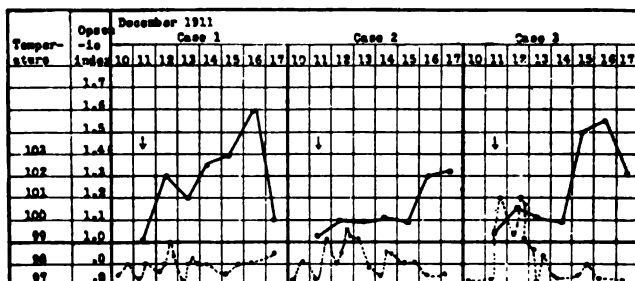


Chart 3.—Opsonic and temperature curves of three persons injected subcutaneously with various doses of autolyzed pneumococci: Continuous line, opsonic index for pneumococci; dotted line, temperature; arrows, time of injections.

#### METHOD OF PREPARATION AND ADMINISTRATION OF THE ANTIGEN

Injections of the extract of pneumococci when highly toxic are followed by marked local reaction, leukocytosis, some fever, and a primary diminution in opsonins followed by a rise.<sup>6</sup> After autolysis has been carried to the point at which most of the toxicity of the extract has disappeared, the local reaction is slight, and antibodies increase more rapidly. The increase in antibodies following injection of the extract is not sustained or as marked as after injection of the partially autolyzed pneumococci (Chart 2). The injection of the former in a small series of cases of pneumonia proved harmless and, at times, beneficial.<sup>7</sup> Hence both extract and autolyzed pneumococci are now used.

The antigen is prepared by growing virulent strains of pneumococci of the different types in tall columns of glucose broth for from eighteen to twenty-four hours, centrifugalizing, and suspending the sediment in

salt solution, so that 1 c.c. contains the growth from approximately 15 c.c. of the culture, that is, about 15 billion pneumococci per cubic centimeter. The suspension of the sediment of the different strains is mixed and then placed in bottles so that the column of liquid is approximately 12 cm. tall. To this a layer 0.5 cm. of ether is added. The bottles are stoppered with sterile corks secured in place by strips of adhesive plaster, thoroughly shaken, and placed at 37 C. The suspension is thoroughly shaken at least twice a day as autolysis proceeds. Immediately after the addition of the ether, and daily thereafter, a small quantity of the suspension is removed and the ether displaced by passing a current of air through the mixture. Films are stained by the Gram method, cultures are made, and intravenous injections are given to guinea-pigs. Autolysis is carried to the point at which approximately 95 per cent of the organisms have become Gram negative and to the point at which 5 c.c. of the suspension produce few or no symptoms in guinea-pigs weighing from 250 to 300 gm. If all the strains are highly virulent, the toxicity of the suspensions usually disappears in from three to five days. When this point has been reached the autolysis is interrupted, the ether removed, and 0.25 per cent cresol or phenol (carbolic acid) added. The antigen is then stored in the ice-chest. It is not used in the treatment of pneumonia until the guinea-pigs injected with the non-toxic suspension have remained well and the cultures sterile for at least ten days. The dose for adults of this antigen should be 1 c.c.; for children, from 0.25 c.c. upward, depending on the age, daily until the temperature becomes normal and remains so for one or two days, or until it is apparent that it has no effect.

#### TREATMENT

The antigen used in the treatment of the 200 cases under consideration consisted of a suspension of approximately 20 billion partially autolyzed pneumococci per cubic centimeter of physiologic sodium chlorid solution. The dose for adults was 1 c.c. daily until the temperature became normal. In children the dose ranged from 0.25 c.c. upward, depending on the age.

The diagnosis was made from the clinical history, character of sputum, physical findings, leukocyte count, etc. Cultures from the sputum were made in many instances, and in a number the type of pneumococcus was determined.

In Table 1 are given the results in the 186 patients that recovered,

and the 14 that died. The results in the 23 patients that received the first injection of antigen on the day of onset were strikingly good in 18, good in 3, and indifferent in 2. The results in the 66 patients receiving the first injection on the second day of onset were strikingly good in 25, good in 34, and indifferent in 7. The results in the 83 patients receiving the first injection on the third day of onset or later were strikingly good in 16, good in 28, and indifferent in 39. The results in the 14 patients in which cases the exact time of the first injection was not recorded were strikingly good in 4, good in 8, and indifferent in 2. Thus in the 186 cases, irrespective of the time of injection, the apparent results were strikingly good in 63, good in 73, and indifferent in 50. Of the 3 fatal cases in which the patients received the first injection on the second day, the apparent results were strikingly good in 1, good in 1, and indifferent in 1, while in the 11 patients who died and who received the first injection on the third day or later the apparent results were indifferent in all.

TABLE 1.—RESULTS OF THE TREATMENT OF LOBAR PNEUMONIA WITH PARTIALLY AUTOLYZED PNEUMOCOCCI

TIME OF FIRST INJECTION	NUMBER OF CASES	APPARENT EFFECT OF ANTIGEN			AVERAGE AGE OF PATIENT
		Strikingly Good	Good	Indifferent	
1. In patients who recovered:					
First day.....	23	18	3	2	32
Second day.....	66	25	34	7	31
Third day or later.....	83	16	28	39	28
Not recorded.....	14	4	8	2	41
Total.....	186	63	73	50	33
2. In patients who died:					
Second day.....	3	1	1	1	58
Third day or later.....	11	0	0	11	44
Total.....	14	1	1	12	51

The average mortality rate in the 95 patients receiving the injection within forty-eight hours after the onset was 3 per cent, while in the 105 receiving the first injection on the third day or later after the onset it was 11 per cent. The total average mortality rate in all cases treated was 7 per cent.

One fatal case showed hemolytic streptococci in the blood and pleural exudate. One was proved to be due to *Bacillus mucosus* and one to *Pneumococcus mucosus*.

This apparently greater benefit following early injection is not due to difference in age, for the average age of the patients in the three groups is thirty-two, thirty-one, and twenty-eight years, respectively. The average age of all the patients who recovered is thirty-three years, while of those who died it is fifty-one years.

In Table 2 is given the time of crisis or lysis in 109 cases in which this could be determined. In the 24 cases in which the first injection was made on the day of onset the average duration of fever was three and one-half days, and in the 32 cases in which the first in-

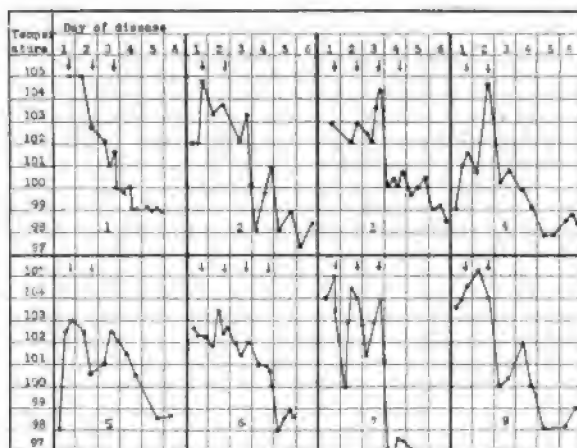


Chart 4.—Temperature curves in eight cases when injections of antigen were begun on the first day of the disease.

jection was given on the second day, the average duration of fever was five days. In the 53 cases in which the first injection was made on the third day or later the average duration of fever was seven days; the total average in the 109 cases was five and two-tenths days.

TABLE 2.—DURATION OF LOBAR PNEUMONIA IN PATIENTS TREATED WITH PARTIALLY AUTOLYZED PNEUMOCOCCI

TIME OF FIRST INJECTION	NUMBER OF CASES	DAY OF CRISIS								AVERAGE DURATION IN DAYS
		2	3	4	5	6	7	8	9 or Later	
First day.....	24	5	9	4	5	1	..	..	..	3.5
Second day.....	32	..	7	7	8	2	4	1	3	5.0
Third day or later.....	53	..	..	4	9	7	15	5	13	7.0
Total.....	109	5	16	15	22	10	19	6	16	5.2

In Charts 4, 5, and 6 are shown representative temperature curves of 22 patients in whose cases the treatment was begun, respectively, on the first, second, and third day or later of the disease. The arrows indicate

the time of injection of antigen. The age in these patients ranged from four and one-half years to fifty-eight years, the average age being twenty-three years. The distribution by lobes was the usual one. In Case 4 the entire left lung of the patient was consolidated. The need for giving the antigen early in the disease in order to obtain evident beneficial effects is well shown in these charts. In Case 16, in which little or no evident effect followed early injection, the patient was a bad alcoholic and had delirium tremens. In many of the patients the onset was violent and the toxemia great. The pulse and respiration rates showed a

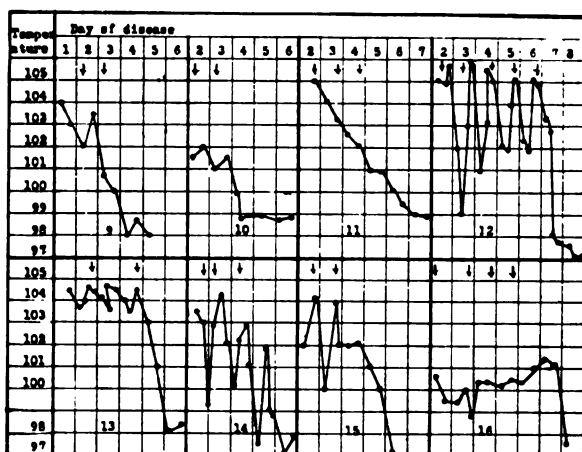


Chart 5.—Temperature curves in eight cases when injections of antigen were begun on the second day of the disease.

corresponding drop with the temperature, and hence the curves are omitted.

In only a relatively few cases was there decided local reaction at the point of injection; in no instances was the injection followed by chill, and no harmful effects have been reported. In some instances there was a short temporary rise in the temperature, followed, especially in the early cases, by a marked drop within twelve hours (Case 9, Chart 5). In some instances, following early injection of antigen, the fall in temperature was abrupt (Cases 1, 2, and 7, Chart 4, and Cases 10, 13, and 15, Chart 5). In others it was more gradual (Cases 5, 6, and 8, Chart 4, and Cases 11, 12, 14, and 15, Chart 5). The drop in the temperature was often more marked following the second early injection after a twenty-four-hour interval than after the first injection (Case 4,

Chart 4, and Case 9, Chart 8). When injections were given late, as shown in Chart 6, the effect on the temperature was less noticeable, although in some instances it began to decline soon after the injections were begun.

The crisis following early injection of the antigen did not differ materially from that which occurs during the natural course of the disease. There was usually an accompanying perspiration, a drop in pulse and respiration rates and in the leukocyte count, and often a most striking disappearance of the toxemia. Resolution of the lung usually occurred quite promptly after the temperature became normal. Extension to another lobe occurred twice in cases in which the antigen was

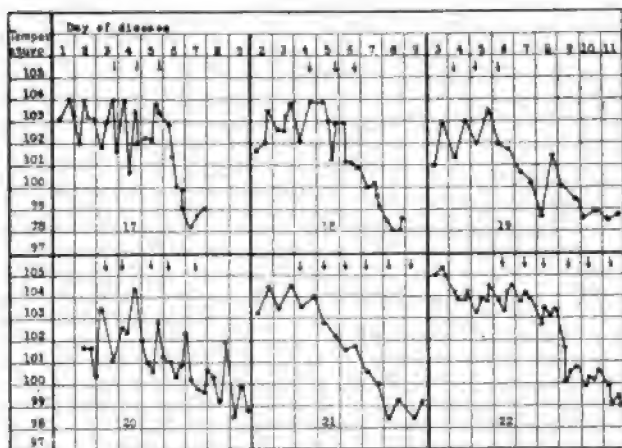


Chart 6.—Temperature curves in six cases when injections of antigen were begun on the third day of the disease or later.

given within forty-eight hours of onset. Empyema developed in only four cases. In three cases of rapidly recurring pneumonia early injections seemed to cut short the attack and, when injections were continued for a time, to prevent recurrence. Apparently good results followed its use in a number of postoperative pneumonias.

The occurrence of early crisis or lysis has been observed in pneumonias due to all of the types of pneumococci, and in at least two cases due to *Pneumococcus mucosus*.

The opinions of some 50 physicians who have coöperated with me are of interest. All but two who used the antigen early in the disease have noted apparently beneficial effects. Those who used the antigen late in



the disease have noted little or no evident action. Those who have treated the largest number of cases with the antigen seem most convinced of its efficacy. Dr. F. Arnold Clarkson, of Toronto, has treated thirteen cases, the patients ranging in age from nineteen to sixty-seven years, without a death during a period when the mortality rate in the remaining cases of pneumonia in the hospital was 50 per cent, and says: "Most of the patients said they felt better for some time after the injection. All recovered, although some of them were very severe on admission to the hospital."

Dr. Ola Putnam, of Marceline, Mo., has reported sixteen cases of pneumonia treated with the antigen, the patients ranging in age from six to sixty-three years, without a death. He says: "When the antigen was used in the first forty-eight hours, the effects were so marked that it does not seem possible to attribute them to coincidence." The results in his hands following the early injection of antigen were so similar to those I have observed for some years that I quote reports of two of his cases:

J. J. D., aged thirty-nine, farmer, weight 200 pounds, married; previous illness consisted of two attacks of renal colic, a few months apart, two years before present illness. Initial chill about 2 A. M., February 14. At 11 A. M. temperature was 103.6, pulse 130, respiration 36, some cyanosis and complaint of pain in left side near nipple. Was expectorating blood-stained sputum; crepitant râles plainly heard over lower lobe of left lung. One c.c. antigen was given hypodermically. The following day about noon temperature was 100, pulse 110, respiration 26, expectoration about the same in quantity and character. One c.c. of antigen was again given and patient had profuse sweat about 9 A. M. The temperature next morning was normal, pulse 76, respiration 24. There was no further rise of temperature, and recovery was uninterrupted.

The case of R. U., forty-two years. One c.c. antigen was given three hours after the initial chill. His temperature was 102.4, pulse 108, respiration 34. There was pleurisy over the lower right lobe, where many crepitant râles could be heard. That night there was some sweating, and twenty-four hours after the first dose of antigen the temperature was normal.

Dr. F. W. Nickel, Eureka, Ill., treated nine cases, the patients ranging in age from two to fifty-eight years. All but three received the first injection on the first day of the disease, with recovery in all. He says: "These cases in which antigen was used, compared to eleven cases in

which it was not used, were milder, average temperature and pulse-rate were lower, they were more comfortable, the duration was shorter, they took nourishment better, and in every way appeared to get along better than the patients treated without antigen during the same period of time—three months (January, February, and March, 1914)."

Dr. J. P. McKelvey, of Pittsburgh, reports three cases, in all of which the antigen was administered late. He writes: "Our results in three cases were rather indifferent, as we were unable to note any definite effect on pulse, temperature, crisis, or general state of the patient."

The exact mode of action of the antigen, whether due to non-specific effects, to desensitization or to the mobilization of antibodies, has not been definitely determined. Considering the experimental and clinical evidence, however, the conclusion seems justified that this antigen, if given early, is followed in lobar pneumonia by the rapid appearance in the blood of demonstrable antibodies and seems to have a definite beneficial action on the disease. Its harmlessness is established. However, owing to the great variations in the course of the disease, depending, among other factors, on the virulence or type of the infecting pneumococcus, it is most difficult to draw conclusions as to the therapeutic value of any agent in pneumonia.

The results presented call for further study and trial. It is hoped that this will be carried out in military hospitals where opportunity to test its efficacy on a large scale under properly controlled conditions is at hand. The serum treatment for Type I infections should, of course, take precedence; but if this serum is not available, the antigen, since polyvalent, should be injected in all cases of pneumonia as soon as the diagnosis can be made. The determination of types of pneumococci, while important, should not prevent its early administration. A large quantity of antigen has been prepared, its effects on animals and on patients tested, and it will be sent on request to physicians in private practice or military hospitals who wish to study its action and who have not the facilities or the necessary time to prepare the antigen.

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\* In connection with elective localization studies it has been the rule to inject intravenously a number of animals with increasing doses of streptococcus cultures. The animals receiving the smaller dose, contrary to expectations, frequently died earlier than those injected with a dose two or three times as large. On studying this point more closely it was found to occur chiefly when freshly isolated strains were grown in glucose broth and when many of the organisms were dead, partially autolyzed, and had become Gram-negative. In other words, dead, partially autolyzed bacteria injected simultaneously with living cultures called forth reactions which tended to protect against infection.

## THE TREATMENT OF EMPYEMA\*

C. A. HEDBLOM

If efficient treatment of empyema were always achieved by the generally accepted drainage operation, there would be little occasion for further discussion of the subject. That such is not the case the constant succession of patients in a chronic condition, always present in any large hospital clinic,—debilitated, deformed, mutilated,—bear ample witness. The high mortality (20 to 30 per cent in adults and 50 to 70 per cent in infants) is indicative not only of the critical conditions in a large proportion of these cases, but also of the relative inadequacy of present-day treatment.

Infected hemothorax or traumatic empyema is, furthermore, the chief cause of death in cases of war wounds of the chest. The mortality due to hemolytic streptococcus empyema in our cantonments has, at some periods, reached 50 per cent. A considerable proportion of such cases also develop chronic empyema.

The profession has not been satisfied with results. The literature describes a large array of apparatus, drainage devices, and modifications of operative procedures, periodically rediscovered. Recently there has been a revival of the almost forgotten antiseptic treatment. It may not be amiss, therefore, to review the subject briefly in its historic aspect.

Intercostal incision or rib resection for drainage was known to the ancients. Hippocrates recognized also variation in virulence of infection, for he taught that "when empyema is treated either by cautery or incision, if pure and white pus flow from the wound the patients recover, but if mixed with blood, stringy, and fetid, they die." With Galen the operation was forgotten. After fourteen centuries, when the works of Hippocrates were again brought to light and when a rational conception of the pathologic anatomy of the process was brought about through postmortem investigation, thoracotomy was again resorted to. The operation was, however, held in great dread. Dupuytren, one of the

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chief advocates of thoracotomy in his day, himself died of empyema. He is credited with having said, "I had rather die at the hand of God than that of the surgeon." With no anesthesia and no antiseptics and a high mortality, one can easily understand how aspiration came to be substituted for thoracotomy. Introduced by Potain, Playfair, and Dieulafoy, it found many adherents. Only after the time of Lister, did thoracotomy again gain acceptance. Roser, in 1865, is credited by Kuster as being the first to adopt it as a regular procedure.

With the antiseptic period date the first attempts at sterilization of the pleural cavity. Carbolic, boric, and salicylic acids, zinc sulphate, zinc chlorid, and iodine were the solutions first used. The iodoform gauze pack was also tried. A Spanish surgeon aspirated pus and injected from 6 to 20 per cent carbolic acid two or three times a day. Frequent collapse, carbolic acid poisoning, and many fatalities discouraged the practice. Murphy's formalin and glycerin injection and Beck's bismuth and vaselin paste have, until recently, remained the representatives of this type of treatment.

The desire to avoid pneumothorax and the frequent resulting collapse of the lung, led to suction drainage, first devised by Buelau in 1876. He introduced a large size catheter through a trocar, the trocar being then withdrawn. The catheter was connected with a dependent rubber tube. The siphon action of the column of pus in the tubing constituted the suction. Perthes' method has been largely used in Europe. Three to five centimeters of one rib are resected and a rubber tube supplied with a collar inserted. The collar is coated with vaselin or cemented fast with collodion. A rubber membrane supplies a certain amount of valve action. Perthes also employed actual suction by connecting the tube to a water faucet exhaust. Cotton, Ware, Roth, and many others have recently devised different modifications of gravity suction water bottles. Schmidt, in 1909, modified the Buelau apparatus by attaching a three-way cannula, one opening leading to an air-pump, one to a manometer for regulating the suction, and the third opening carrying off the pus.

One shortcoming of this type of drainage is the leak that soon begins from pressure necrosis of the tissue surrounding the tube, whether the drainage is introduced through a trocar or sutured into a thoracotomy wound. Robinson attempted to correct the fault by screwing a threaded cannula into a trephine opening in a rib. This maintains a tight joint for a week or ten days.

Open pneumothorax, collapse of the lung, and the chronic cavity often resulting from wide open drainage, led to the adoption of valve-like arrangements allowing for the escape of pus during expiration, but closing the wound during inspiration. To this end Cabot, in 1880, applied a piece of sheet-rubber over the wound. This principle has since had many advocates. Cotton recommends cementing the membrane on three sides. Lund fashions a skin-flap from above the rib to be resected, and places the slanting opening of the drainage-tube in such a position that on inspiration the skin-flap occludes the lumen. Baylor describes a rubber valve in a metal tube, Hutton, a gutta-percha nipple slit at the end and inserted in a glass tube, and Williams, an ordinary rubber valve. Boinet devised a "flutter-valve" at the end of an ordinary drainage-tube. The so-called ventilation drain of Tiegel consisted of a piece of lead tubing bent to fit the pleural cavity and provided with a valve. Ransohoff fits a very thin rubber tube around an ordinary drainage-tube. Pus escapes readily but the suction effect of inspiration collapses the outer tube.

One form of valve, which probably has many cures to its credit, is the neglected, pus-soaked dressing. There is no doubt that a large number of patients, probably the majority, get well without complications, following ample rib resection and stiff tube drainage. Cotton writes: "I believe absolutely that most empyemas get well by accident—get well because a sloppy, pus-soaked gauze dressing is a very fair valve."

Seidel, in 1907, described an apparatus consisting of a glass hemisphere applied over the wound and the air exhausted by Perthes' water-pump method. Nordmann, the same year, before a continental surgical congress, demonstrated an aspirating apparatus on the same order, and provided with a manometer and air pump. He claimed for his apparatus portability and easily controlled degree of suction. It is cemented to the skin with collodion or gum arabic, and may be left on from ten to twelve days. It is usually changed every three to four days. Suction the first day is kept at from 5 to 10 mm. mercury, the second day from 10 to 25 mm. Further rarefaction is regulated according to the patient's feeling of discomfort or pain. In acute empyema, from 120 to 150 mm. is reached in from one and one-half to two weeks; in chronic cases this amount is reached at once. From a mechanical point of view, this apparatus would seem efficiently to meet the requirements of a continuous negative pressure. Lawrow reports an elaborate study of nineteen acute cases treated with this apparatus. Aspiration was

continued from twelve to seventy-four days, the average being thirty-five and one-half days. An average of eighty-eight days was the time required to effect a cure in his most favorable cases.

A critical evaluation of the comparative merits of these methods seems almost impossible. However, the fact is significant that no one of them has been generally accepted as conspicuously superior.

Departures from the routine operative procedure have been made from time to time. Revilliod, in about 1890, according to Lawrow, advocated wide-open thoracotomy, the removal of fibrin, and tight closure of the thorax to the drain. Lloyd, in 1896, reported the result of a similar radical operation in 225 cases, with a mortality of 20 per cent. Sauerbruch, in 1908, reported two cases of acute empyema in which operation was done under differential pressure and tight closure after evacuating the pus, with favorable results. Willy Meyer, on the contrary, operated on three patients, in two of which pocketing occurred, necessitating a second operation. Fresh interest is attached to this treatment in view of the apparently successful tight closures of leaking wounds and of infected hemothorax at the battle front. Lilienthal has recently elaborated a modification of Lloyd's operation, which he calls major thoracotomy. It consists in general anesthesia, wide intercostal incision, rib spreading exposure, the "mobilizing" of the lung by the hand inside the thorax, freeing adhesions, and removing fibrin. The wound is closed tightly to rubber tissue wicks at the angles. In September, 1917, Lilienthal reported forty-four such operations with a mortality of 27.2 per cent. One-third of the operations were performed after a preliminary aspiration. The mortality in thirty-eight patients operated on by minor thoracotomy—ordinary rib resection or intercostal incision—was 18.4 per cent. No thoracoplasty was necessary in any of these cases. In the preceding ten years, 258 patients were operated on, with a mortality of 23 per cent. Collapsing thoracoplasties were performed in 15 per cent of the cases. Lilienthal writes, "There have been a number of revisions, secondary and even tertiary, but eventually all patients were sent home with symmetric chests and fully expanded lungs." Whittemore, at the Massachusetts General Hospital, reports twelve cases, with one death in forty-eight hours from cerebral embolus. In two instances the lung did not fully expand. Whittemore operates under intratracheal anesthesia, which he believes materially aids in obtaining full lung expansion.

A revival of the generally discarded treatment of empyema with

antiseptics was initiated with the Carrel-Dakin method. Before the Section on Thoracic Surgery at the meeting of the American Medical Association this year Major Stewart, of the War Demonstration Hospital of the Rockefeller Institute, reported cases of 44 patients treated by this method. Ordinary rib resection was followed by the introduction of from three to five Carrel tubes, rendered stiff by silver wire. An ordinary drainage-tube was also used to carry off the surplus Dakin fluid. Instillations of from 30 to 100 c.c. in the first cases every two hours, then every hour during the day and every two hours at night, resulted in sterilization in from four to fourteen days. The wounds closed spontaneously or were sutured, the latter on an average of the fourteenth day. There were twelve deaths in the series, a mortality of 27 per cent. Variations have been made in technic and in the use of the Dakin solution, and favorable results have been reported by Campbell, De Page, Tuffier, and others.

The hemolytic streptococcus empyema epidemic during the past eight months in our cantonments presents an apparently new aspect of the problem. Streptococcus empyema has not been uncommon in the past. In a series of 574 pleural exudates examined at the Mt. Sinai Hospital, streptococcus occurred in about 23 per cent. In this same series of 66 cases of pneumococcus infections there were 14 deaths. In 30 cases of streptococcus infections there were no deaths. The occurrence of hemolytic streptococcus is not mentioned. Except in tuberculous and actinomycetic infection, the treatment has, in the past, been but little influenced by the bacteriologic findings. In 1910 Robinson wrote, "Every unilateral empyema should be drained by an operation, whether the material obtained in diagnostic thoracentesis is pure pneumococcus, staphylococcus, streptococcus, or the three combined." In the hemolytic streptococcus infections in our cantonments it has been different. The frightful mortality from streptococcus empyema following measles and bronchopneumonia is known to all. From Camp Zachary Taylor, Hamburger and Mayers reported that of 388 cases of measles 77.1 per cent were streptococcus carriers, as determined by throat swabs. Of 162 hemolytic streptococcus carriers 45 developed bronchopneumonia, 33 per cent of whom had empyema. At the same camp, from the middle of December to the middle of January, there were 109 cases of pneumonia and 52, almost 50 per cent, of empyema. Christmas week of that period 18 cases of empyema developed, and in spite of treatment there were 15 deaths. Many of the patients came in with a



chest full of pus, that twenty-four hours before the x-ray had demonstrated to be free of fluid. Of 86 patients, 20 died, 6 were discharged to duty, and 60 remained under treatment at the time the report was written. Rib resection was found ineffectual. No patient having this type of treatment had left the hospital, while 9 thus treated were dead. Suction drainage gave the best results. The exploratory tap was followed in several instances by serious collapse, and there was one sudden death explained on the basis of vagosympathetic reflex. Following a change in technic in which 0.5 per cent cocain was used and the pus withdrawn through the same needle, there were no further untoward symptoms of this kind. Some patients were worse twenty-four hours after aspiration, having rapid, thready pulse, drenching perspiration, clammy skin, and other symptoms of overwhelming toxemia. This was attributed to the sudden withdrawal of too much fluid.

At Fort Riley empyema occurred in 21 per cent of 900 cases of pneumonia. Early operation resulted in a high mortality. Preliminary aspiration and intrapleural lavage lowered the mortality. Some patients recovered without operation. In such epidemics, therefore, the bacterial findings seem to be of great significance, not only from a diagnostic standpoint, but also from that of treatment. The variable hemolytic property of the streptococcus, with which apparently the virulence largely is associated, further makes the bacteriologic study far more complex than it has been believed. Questions of epidemiology of mutations in the organism, of when to aspirate and when to resect, of antiseptics, and of serum and vaccine therapy, render the treatment of this type of empyema anything but simple.

Some idea of the importance of traumatic empyema as seen at the battle front is gained from a consideration of the fact that three-fourths of all the chest wounds are penetrating in the sense that they pierce the parietal pleura. The grave probability of the development of sepsis is often alluded to. The battlefield of Flanders and of northern France is described as a sea of mud in winter and worse than a sandstorm in the desert in summer, and at no time has the contact between soil and soldier been closer or more lingering. Bullets, and especially jagged shell fragments, carry in with them bits of skin and clothing plastered with this bacteria-infected dirt, and infection would seem almost inevitable. Special conditions tending to the development of sepsis are open sucking wounds, present in 20 to 30 per cent of the cases. These may become infected by direct extension. A second group of cases are those

of a retained foreign body. In one series of 131 cases there were 74 bullet wounds and 57 shell wounds. About 20 per cent of the bullets and 50 per cent of the shell fragments were retained. A third of the bullet wounds and almost three-fourths of the shell wounds become infected. A third group are those with associated hemothorax. About two-thirds of the cases of penetrating wounds develop hemothorax, and about 25 per cent of all cases of hemothorax, according to Elliot, become septic. In 153 of his own cases 40 per cent were infected. The incubative period varies. Fulminating sepsis may develop in forty-eight hours. The onset of the symptoms is often gradual and insidious. The gross characteristics of the aspirated fluid are not a safe indicator as to whether or not the blood is sterile. The surest early sign of bacterial growth is a foul odor. The first puncture may fail to produce a growth. Elliot and Henry found that the first diagnostic puncture was negative in 50 per cent of cases of anaërobic infection. Moynihan states that the upper part of the fluid may be sterile and the lower layers positive to culture.

Pocketing of the fluid also occurs. The gross characteristics of the fluid may be misleading. It may resemble normal blood and yet teem with bacteria. Anaërobic infection occurs in from 40 to 50 per cent, so that cultures must be made under both aerobic and anaërobic conditions. The bacteria are often of fecal origin. The prognosis has been bad. According to Elliot, 50 of 100 patients will die, and in 17 of the 50 who survive the condition will become chronic. Of the remaining 33, 16 will be invalided six months or more. Only one out of eight has good prospects for immediate recovery.

Treatment under such conditions can hardly be too drastic, if curative. The aspiration of sterile hemothorax or thoracotomy, and turning out of clotted blood, lessens the incidence of sepsis. Early recognition and prompt, efficient drainage are imperative. The only means of making sure of infection in the absence of pus is by culture. In critically ill patients preliminary evacuation of pus by aspiration is advised. Both local and general anesthesia have their advocates. A few months since Moynihan wrote that Tuffier has modified, profoundly for the better, the treatment of these trying cases by adapting to their needs the Carrel-Dakin technic as herein outlined. Dichloramin-T is considered by Carrel of less benefit because it does not dissolve the septic sloughing tissue. Eusol, Bipp, Flavine, etc., have also been used, followed in some cases by immediate tight closure of the chest without drainage.

Of one series of 29 cases so treated, in 16 the chest remained closed. In these cases the patients are aspirated forty-eight hours after closure. It may be that the treatment of infection of the chest will shift to closure without preliminary antiseptics, as seems to be the case in the treatment of other war wounds. Thus Surgeon General Sir Anthony Bowlby, in March of the present year, writes: "At the last meeting of the Surgical Conference of the Allies in Paris, May, 1917, it was agreed that operation in some instances should be followed by primary closure of the wound, notably in case of wounded joints. But in the following November the conclusion arrived at was: Since our last session the disinfection of wounds has passed from the domain of the chemist to that of the surgeon. Primary suture has taken the place of secondary suture, and has become the method of choice."

In the treatment of infected hemothorax Moynihan advocates wide-open thoracotomy in order to wash out clots, remove the foreign body, disinfect the cavity, and establish drainage by a stab puncture or small rib resection below. He says: "This is only to bring the treatment of wounds of the lung into line with that practised elsewhere. The surgeon no longer allows infection to be well established in the wound; his aim is to attack by approved methods (the free opening of the wound, the excision of all dead or contaminated tissue, the removal of all fragments of clothing, of all projectiles and of all foreign bodies), and then to secure the earliest possible closure of the wound which remains. No less an ideal and no less scrupulous a practice would guide him also in the treatment of wounds of the lung and pleura. The time has gone by when he can justly allow infection to become deeply ingrained before adopting those tardy, incomplete, and often ineffective methods with which he has been too long content."

The question of the application of these principles to civil practice is an important one. The progress in abdominal surgery really began, as it is often pointed out, by letting in the light. The trend in the treatment of chest conditions in general, and of acute empyema in particular, is in this direction, and results thus far seem promising.

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## CHONDROMA OF THE THORAX\*

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Chondromas may be found fairly often throughout the several portions of the body that contain cartilage or its homologue, but such growths within the thoracic wall are so infrequent as to excite more than ordinary interest. A patient was recently observed in the Mayo Clinic who had a hard tumor in the pleural cavity. The findings were briefly as follows:

*History.*—Case 249165, a man aged sixty-one, gave a history of having had an intrathoracic tumor for twenty-five years. The tumor extended downward from its attachment on the first rib to a point well below the fourth rib, and when first noticed, was bulging the chest-wall outward at that point. In 1895 Dr. Christian Fenger had removed a small growth from one of the ribs in the region of the axilla and reported a benign tumor made up of cartilage and bony tissue. No radiographic record of the case was made at that time. Throughout the years since then the patient, who is a dentist, was able to go about his work unembarrassed by the presence of the tumor until one year previously, when movement of the arms caused intercostal pain. This pain on motion was augmented by a very tender mass over the juncture of the gladiolus and xiphoid sternum, which had grown noticeably during the past year. On physical examination the tender areas could be felt along the ribs with several enlargements of bone-like consistency, both in the ribs and in the sternum. The primary tumor was easily mapped out; it filled the area in the right upper thorax as described, and was of varying degrees of hardness, as evidenced by the varying percussion-note on examination. Signs of pressure were manifested by engorged veins, an enlarged right arm, and neuralgic pains. Fluoroscopic examination revealed many small tumors in the ribs and in the sternum, and the large primary tumor, pedunculated and attached to the first rib, could be seen moving with the respiratory excursions. Other findings were negative except that the urine showed Bence-Jones albumin positive. There had been a loss of 20 pounds in weight in the last year. An exploration was made through an incision over the tumor just below the fold of the

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pectoralis major. Segments of the hard tumor were removed with a rongeur for microscopic examination, which revealed calcareous necrotic tissue. The large tumor in the pleural sac could have been resected, but such an operation would necessarily have been severe and difficult, and in the presence of multiple tumors, perhaps secondary growths, which could not be removed, the operation was thought an unwise procedure. The patient was sent to his home with instructions to take Coolidge tube treatments. The probability of malignancy, even if inconclusive, is very strong.

*Discussion.*—It could not be determined whether or not the rib and sternal tumors were secondaries, but their recent growth, their pressure on the nerves, and the consequent neuralgia would lend credence to that assumption, as would the fact that the patient had lost 20 pounds in weight and had Bence-Jones albumin in the urine. This last finding is, however, of rather doubtful significance, since its value as a test for malignancy is not established, although it is known to be one of the early findings in cases of myeloma. Because of the size of the mass it is presumable that it would show degenerative changes at the central zones, for example, those farthest removed from the source of nutrition. It might be mentioned that this patient had sustained an injury to the chest forty years previously. That such intrathoracic tumors occur but rarely is evidenced by the fact that this is the only case observed in the routine examination of 250,000 patients in the Mayo Clinic.

Busse, in 1907, reported a case of a tumor of the pleura and mentioned those described by Schultze, von Reissig, Lesser, Turner, and others. In Schultze's case, in a man sixty-nine years of age, the tumor was found in the pleura; it was kidney-shaped and lay in a sac composed of visceral pleura. Secondary cartilaginous pea-shaped bodies had formed in the apex of the lung. In von Reissig's case the tumor was smaller—the size of a cherry; a like body was found in the visceral pleura and it contained connective tissue, adipose tissue, and also true bone tissue. It was believed that the tumor had developed from the endothelium itself. In the case described by Lesser the tumor was 15 by 5.5 by 2.5 cm. in size, and was found in the lower lobe of the left lung. It contained cartilage and true bone, with Haversian canals. In Turner's case the tumor had developed from the sternum, a fairly common site, thence had grown into the chest cavity, pushing the heart to the right and compressing the left lung in its development. It showed the well-recognized tendency toward degeneration in its interior, the degenerated tissue being replaced by calcareous deposit.

Parham, in 1899, collected the literature of 78 cases of chondroma of the chest, and described tumors that had developed in the ribs and sternum and pushed their way into the thoracic cavity. In his report, quoting Weber and Schläpfer's 260 cases, he stated that 3 per cent of chondromas or osteochondromas develop primarily in the rib.

Adami has classified chondromas as hylic or pulp tumors of mesenchymal origin and typical in character, because they resemble in struc-



Fig. 301 (249165).—Chondroma of the thorax.

ture the tissues from which they develop. White places them among the histiomas or tissue tumors. They may be single or multiple and are usually globular in shape, surrounded by a fibrous capsule, the result of long-continued pressure on the surrounding tissues. Such tumors do not infiltrate unless they become atypical or sarcomatous. Most of the growths described as chondromas or ecchondromas are really not isolated tumors growing independently of the mother tissue, and should properly be classified, as Adami suggests, under the head of ecchon-

dromas or chondromatoid growths. True echondromas are found lying free and encapsulated in the long bones, salivary glands, and in the glands of reproduction. There may be some doubt regarding these so-called mixed tumors of the testes and of the parotid, because they have been found to be derived from all three primary germinal layers and are not alone mesenchymal in origin. Kettle, in this connection, mentions the often-quoted tumor of Paget, which was later proved by Nicholson to be a teratoma. Kettle makes the observation that "With this example before us we should, I think, regard with some suspicion the formation of metastases by a simple chondroma."

The echondromas are derived from regions in which cartilage exists, and are found in the ribs, in the larynx, in the trachea, and in the intervertebral discs. A number of such laryngeal and tracheal tumors have been observed in the Mayo Clinic by New. The chondromatoid tumors are usually lobulated, the lobules being separated by bands of connective tissue which carry the blood-vessels and lymphatics into the interior of the developing growth, in which there are to be found few vessels or none at all. Because of this separation of the interior of such tumors from their supply base, degeneration is likely to take place, and thus it is that at the central areas degenerating processes pass through all the types from mucoid or myxomatous to calcareous or even to true bone formations, as in Lesser's and Turner's cases. In the last type bone-like masses are more often found than true bone, although in the case herein reported a tissue bearing true bone cells and Haversian canals was demonstrated (Fig. 301).

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## FRACTURES OF THE NECK OF THE FEMUR\*

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Fractures of the neck of the femur are the most disabling to the elderly, and constitute one-third of all the fractures in people more than seventy years of age. There has been handed down to us one hundred years of tradition, due to the teachings of Sir Astley Cooper, that bony union is a rarity following such a fracture, and that treatment, particularly of the subcapital or so-called intracapsular fracture, is well-nigh hopeless. Such teaching has produced, to say the least, a cursory type of treatment, with disastrous results. Occurring, as such fractures often do, in old age, many persons end their days in pain and suffering when they might have had days of comfort and peace.

The current medical literature of recent years has, from time to time, contained excellent papers calling attention to the success that may be expected to follow treatment based on a sound pathologic knowledge of the fracture under discussion. Because in isolated instances elderly persons have died following fractures of the hip, an exaggerated view of the mortality rate has been held. Whitman cites statistics from Bellevue Hospital, New York, showing that in 241 consecutive cases treated in three years there were but three deaths—one within twenty-four hours, which may have been due to fat embolism, and two due to alcoholism and nephritis. These figures show that as a group such patients are entitled to active treatment, instead of the "let alone" method, which is almost sure to give poor results.

Fractures of the hip may be produced by muscular action or some slight jar or jolt, such as slipping off a curb or a low step. Fractures happening in this manner are found in the aged, although occasionally seen as the first manifestation of a Charcot joint in young persons. Close questioning in the latter cases may be necessary to elicit the information that the hip seemed to give way, causing the fall, that is, the

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fall was caused by the break and not the break by the fall. The majority of fractures of the hip are, however, produced by direct violence, usually by a fall on the trochanter.

As a basis for this communication 165 consecutive case histories of patients coming to the Mayo Clinic for fracture of the neck of the femur have been studied. There were 66 females and 99 males. The ages of the patients at the time of accident varied and showed that the condition is by no means confined to the elderly. There were 11 between ten and twenty years, 18 between twenty and thirty, 27 between thirty and forty, 26 between forty and fifty, 51 between fifty and sixty, 24 between sixty and seventy, 5 between seventy and eighty, 3 between eighty and ninety. A large majority of the series had old, ununited fractures, the patient coming for treatment three or four months or as many years after the accident. The number emphasizes in general either that the treatment of fractures of the hip is very poor or that the condition is a very difficult one to treat. Because of the great length of time that had elapsed between the accident and our examination it was impossible to determine whether the type of fracture was originally subcapital (intracapsular) or trochanteric (extracapsular). The impression was gained, however, that it is not alone the subcapital type in which there is non-union. If it is true that a fall from a height on the feet produces a fracture of the neck of the femur of the subcapital type, and that an injury in which the force is applied directly to the trochanter, as in a fall on the hip, produces a trochanteric type of fracture, then many of these cases of non-union must have followed the trochanteric type of fracture. After the accident there are pain and disability, usually total, shortening and eversion, and the trochanter and upper part of the femur sag to a more posterior plane than the same region of the opposite leg. The problem the surgeon is confronted with is to reestablish normal length, correct the eversion and raise the trochanter forward, and once these conditions are fulfilled, to hold the corrected position. It is the last requirement which has brought out the different methods of treatment.

Brief mention will be made of four methods, any one of which, properly carried out, will give good results in fractures of the neck of the femur, be the fracture subcapital (intracapsular) or trochanteric (extracapsular). One hundred per cent good results cannot be expected, since no surgical procedure gives such a percentage, but the cases show that very much better results can be obtained by these methods than by any other.

The outstanding features of a review of our case histories were that in a great many instances the diagnosis was not made until too late for efficient primary measures, and that even when the diagnosis was correctly made, the treatment accorded as a whole was woefully inefficient. Many had no treatment at all, a diagnosis never having been made. Following the accident there may have been a weak impaction disguising the symptoms; repeated examinations were not made subsequent to a diagnosis of sprain; the impaction broke down and only when too late

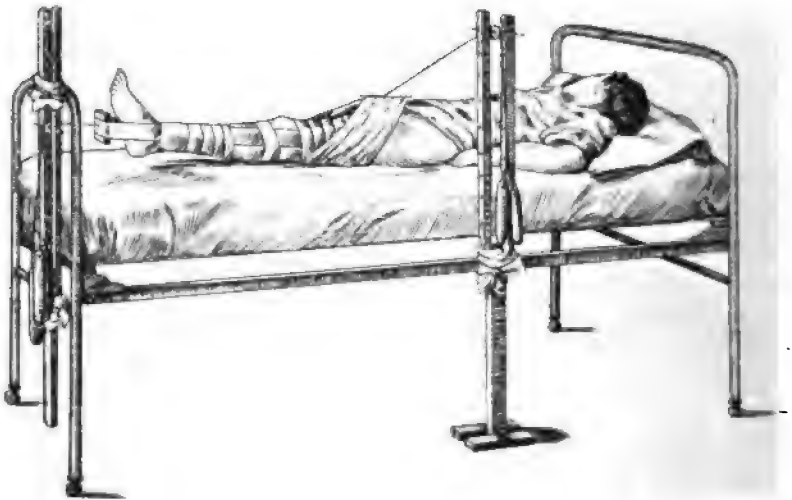


Fig. 302.—The Ruth-Maxwell method. Longitudinal, lateral, and forward traction.

did the examination, most often by another physician, disclose the typical signs of fracture of the hip.

In all our text-books runs the warning against breaking up a so-called impacted fracture, and perhaps no one rule has done more to cause many poor results. Once the term impacted is applied to the case, it gives all concerned a sense of unjustified security. It is most difficult to tell whether a fracture of the neck of the femur is securely impacted. Whitman describes this very well when he says, "What passes for impaction is usually a fracture with but slight displacement; clinically a case in

which shortening is slight, in which crepitus is absent, and in which some control of motion or even capacity for weight bearing is retained." It is best in every case that the impaction should be broken up, and this is advised by such authorities as Jones, Whitman, and Ruth.

In 1869 Dr. Phillips, of Dixon, Illinois, first used what is now known as the Ruth-Maxwell method. Dr. Maxwell advocated it, and following him Dr. C. E. Ruth, both preferring to call it the anatomic method. Ruth advises, as the first step in the treatment, flexing the thigh, thus permitting disengagement of the fractured surfaces. The leg should then be forcibly straightened, the traction being persistent, strong, and steady until the normal length is secured. The eversion should be corrected and the trochanter forced up to its proper place, when a Buck's

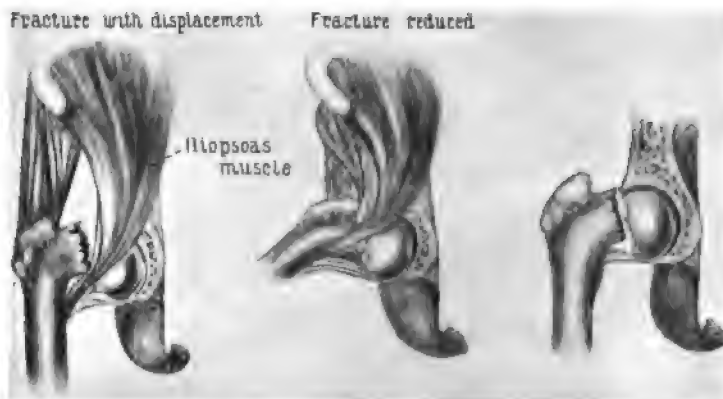


Fig. 303.—Diagrammatic representation of reduced fracture of the hip, held in place by abduction (Whitman)

extension should be applied with a weight of 20 pounds for the ordinary individual (Fig. 302). A binder's board or fiber should be molded to the inner and upper side of the thigh, over which a band of muslin four to six inches wide should be passed outward, slightly upward, and sufficiently forward so that the weight of this counterextension overcomes the internal pull of all the rotators and adductors, and at the same time raises the lower fragment to its normal level. This weight varies from 5 to 15 pounds. If in addition this method is further modified so that the leg is kept in abduction, better coaptation of the fragments is insured. Whitman states that Ruth has modified his treatment in this manner, thus accepting the position of abduction as an aid to the treatment.

The method advocated by Whitman is based on the fact that if a

fresh fracture of the neck of the femur is reduced and the limb placed in the normal position, reëstablishing length and overcoming the external rotation and backward displacement of the trochanter, the fractured surfaces may very readily be held in this relation by abducting the hip to an angle of approximately 45 degrees (Fig. 303). This is the extreme abduction normally permitted, and it forcibly impacts the fractured surface of the neck against the fractured surface of the head of the femur. The exact method, according to Whitman, is as follows: "The patient having been anesthetized, is lifted to a sacral support, the shoulders resting on a box of equal height while the extended limbs are sup-



Fig. 304.—Subcapital fracture of the neck of the femur in a woman aged fifty.

ported by two assistants. The assistant holding the sound limb then abducts it to the anatomic limit to illustrate the normal range, which varies in different individuals and at different ages, and, incidentally, to fix the pelvis by direct bony contact. The operator first flexes the thigh of the affected leg to disengage the fragments. The assistant then extends the limb and by manual traction overcomes the shortening, as demonstrated by the relation of the trochanter to Nélaton's line and by measurements. He then rotates it inward, and, under traction, abducts it to the normal limit, the operator meanwhile lifting the thigh

and trochanter from beneath. Inspection should now show absolute correspondence between the extended limbs as to abduction, rotation, length, and position of the trochanter. In this attitude the injured part is securely fixed by a plaster spica extending from the nipples to the toes." Patients treated in this manner may readily be moved and their position in bed altered, as the extreme abduction absolutely prohibits any motion of the fragments and does not permit joint fluid to find its way between the surfaces.

Cotton in his method uses practically the same procedure, except that after he has broken down the impaction and reduced the fracture



Fig. 305.—Same as Figure 304, after the reduction by the Whitman abduction method.

he aims firmly to impact the fragments with the leg in abduction by hammering on the trochanter with a padded mallet driving the outer fragment into the inner. With this accomplished, he uses a plaster-of-Paris cast to hold the position.

Sir Robert Jones applies the same anatomic principles, but uses his abduction frame to control the fragments. In his skilled hands it is an excellent fixative apparatus, but attention is necessary to see that no kind-hearted but meddlesome attendant loosens a strap or changes the position of the patient in the attempt to make him more comfortable,

so that fixation is altered and mischief done. Following such treatment it is necessary to maintain fixation of the fractured surfaces for three months, and not to permit any weight-bearing for six months (Figs. 304 and 305). These methods may be considered as conservative surgical measures, and the cases reported by their originators show that bony union with normally functioning limbs can be obtained (Figs. 305 and 306). In skilled hands and with careful technic there can be no doubt that an open operation and the placing of an autogenous or heterogeneous bone peg through the trochanter and neck into the head of the



Fig. 306.—Trochanteric fracture of the neck of the femur in a woman aged fifty-six.

femur, followed by adequate fixation, would give excellent results, but the results in fresh fractures are so good by the former methods that more radical procedure is not necessary.

In the large number of patients with ununited fractures of the hip observed in the Mayo Clinic radical surgery has been resorted to in 33 (Figs. 307, 308 and 309). The ages of those operated on were as follows: One between ten and twenty years, 3 between twenty-one and thirty, 9 between thirty-one and forty, 7 between forty-one and fifty, eleven between fifty-one and sixty, and 2 between sixty-one and seventy. Nine were females and 24 were males. There were no deaths. The



Fig. 307.—Same as Figure 306, after reduction by the Ruth-Maxwell method, followed in three weeks by abducted position in plaster-of-Paris cast.



Fig. 308.—Ununited fracture of the neck of the femur with absorption of the neck one year after accident. (Man, aged forty-nine.)



number is too small satisfactorily to draw conclusions from any statistics that might be compiled, therefore the present report can be of value only by somewhat arbitrarily stating conclusions based on clinical observations. Various measures were adopted. In a number of cases nails and screws were used. The attempt to place these without exposing and freshening the fractured surfaces practically means failure, and was early abandoned, and even after freshening the surfaces the final results were poor. The last 17 patients were subjected to some form of bone grafting. The bone peg has been employed in four ways:



Fig. 309.—Bone peg from the tibia in place.

1. As an autogenous peg taken from the patient's tibia on the affected limb, and, after freshening the fractured surfaces, placed through the trochanter and what was left of the neck into the head of the bone.

2. As smaller autogenous grafts wedged in between the fractured surfaces. A piece of bone five or six inches in length removed from the tibia was sawed into three pieces, which were placed either vertically or horizontally between the fractured surfaces and wedged firmly between the fragments by placing the limb in abduction. It was hoped in this manner to restore at least some of the absorbed neck of the bone.

3. As heterogeneous bone pegs obtained by taking beef bone and turning out on the lathe threaded pegs of suitable size.



Fig. 310.—Bone peg atrophied and fractured three months after operation.



Fig. 311.—Ununited fracture of the neck of the femur one year after the accident. Marked absorption of the neck. (Man, aged thirty-three.)

4. The fibula used, according to the advice of Davison, as a peg.

In nine cases in which the bone graft was tibial and autogenous, used either as a large peg or as multiple small grafts, there were but two successes. At first it was thought that failure was due to inadequate fixation in that it was not prolonged enough, but even after three months' fixation the peg broke, and most of the pegs broke while the cast was still being worn (Figs. 311, 312, and 313). In no case was there any evidence shown in the radiogram that the graft increased in size to take on function. On the contrary, the graft atrophied and broke where it bridged



Fig. 312.—Fibula used as bone peg. Bony union secured.

the fracture line. As these grafts were all cortical bone, and were placed in cancellus bone, we believed that they were gradually replaced by bone natural to the situation, and that in this process of substitution the pull of the powerful muscles on the lower fragment, even when in a cast, was sufficient to break the weakened graft where it crossed the fracture line. We have used the fibula in six cases with three successes. It has advantages over the other grafts in that it is large, strong, and has the full thickness of bone (Fig. 312). The entire thickness of the fibula of the desired length is removed, usually at the juncture of the lower with the middle third. The removal is done subperiosteally as much as

possible, and before the bone is used as a peg the remaining muscle tags and periosteum are removed. The bony defect in the fibula does not completely regenerate, but causes no inconvenience to the patient, and function is perfect. The beef peg has been used four times with two successes, but it is only fair to state that these two were especially favorable cases for operation, and bony union probably would have resulted without the operation, although not so rapidly. From our experience we are inclined to discontinue the use of such a peg in old ununited fractures, particularly in elderly persons. If operation is advised in a



Fig. 313.—Fracture of the neck of the femur in a man aged twenty-seven. Non-union of two months' standing.

recent case or in a young person, a beef peg would be quite suitable (Figs. 313, 314, and 315).

In our work we have used the approach advised by Murphy, that is, the curved incision over the trochanter with the broad base upward and the bottom of the U passing across the femur two inches below the tip of the trochanter. On reflecting this flap upward the tip of the trochanter, with its attached muscles, is either sawed off with a Gigli saw or chiseled free and also reflected upward. Ready approach to the neck of the femur is then secured. The fractured surfaces are exposed

and freshened, and whatever means the surgeon prefers is used to hold them together.

The results of our efforts in these 33 cases were disappointing, there being 7 successes and 26 failures. The operation step by step is not difficult, but taken as a whole, consisting of the exposure, the freshening of the bony surfaces, the placing of the graft in such a way that it is at a mechanical advantage, the holding of the position while the wound is being closed, and the fixation, usually plaster-of-Paris, is applied, devolves considerable difficulty on the surgeon, making the entire opera-



Fig. 314.—Surface freshened and held in place by beef bone peg, two months after operation.

tion somewhat formidable. In some cases the failure was undoubtedly due to faulty technic, poor placing of the nails, screws, or bone grafts; in others the fault probably lay in poor post-operative fixation.

While in the main our results were disappointing, we had some successes. It must be remembered that as a group these patients had nothing to look forward to but continued disability, and the attempt was justifiable. From the experience gained we could probably obtain better results in the next 33 cases. The selection of the cases for operation is most important. The more of the neck of the femur that is absorbed, the poorer the chance of obtaining bony union by surgical measures.

The older the patient, other things being equal, the poorer the prognosis. An older patient might, however, offer better chances for surgery if more of the neck of the femur were present than would a young patient with no femoral neck. One of our patients, a young woman twenty-five years of age, in six months after the accident showed complete absence of the neck of the femur, and the operation was of no benefit.

The poor showing of our surgical efforts in this group of ununited fractures of the hip serves but to emphasize most strongly the necessity for rational adequate therapeutics immediately following the fracture.



Fig. 315.—Same as Figures 313 and 314, four months after operation. Bony union complete.

If radical surgery must be attempted, we would advise, as the result of our experience, that a bone graft, preferably the fibula, be used, though even this procedure is uncertain. Too much emphasis cannot be laid on the necessity of applying proper treatment immediately after the accident, thus not allowing the patient to go on to the most distressing condition of non-union.

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in the diagnosis of, and the differentiation between, single and multiple cystic disease. Heineke, in 1903, reported its use in his cases; previous to that time most material was reported from necropsy findings. Cysts frequently are discovered only after fracture, and the radiograph, as commonly used today, aids materially in the early diagnosis.

The etiology of fibrocystic formation is obscure, the general fibrocystic types especially remaining unsolved. The theory of trauma is most generally accepted, but there are reasons for believing infection to be the etiologic factor. The theory of inflammation has many adherents, and culture material gathered in the future should be given thorough study.

#### TYPES

1. Cystic degeneration of enchondroma, etc., single or multiple (Virchow).
2. Callous, subperiosteal, etc. Hematoma, traumatic.
3. Cysts occurring in osteomalacia.
4. Cysts occurring in Paget's disease (osteitis deformans).
5. Localized osteitis fibrosa cystica.
6. General osteitis fibrosa cystica (von Recklinghausen).
7. Echinococcus and cysticercus.
8. Dentigerous.
9. Cysts occurring from mercurial poisoning.
10. Cysts resulting from infection.

Virchow's theory, while possible, has now been generally discarded, cartilage being found in varying quantity in the different types and looked on as a part of the metaplastic process. Von Recklinghausen believed trauma and mechanical factors were the probable causes of the production of osteitis fibrosa cystica and that it was pathologically impossible to differentiate between osteomalacia, Paget's disease, cysts, etc., and osteitis fibrosa. Boit believes that the changes result from toxic, metabolic, traumatic, or infectious processes and derangement of internal secretions. Rehn believes that the process is not an entity but a phase of dystrophy in rapidly growing bones, and likens it to the disease known as snuffles in the hog, using the term *osteodystrophy deformans infantilis* and *senilis*. Ropke and Lubarsch report the finding of organisms and ascribe the formation of cysts to infection, a view held by Murphy and others. (Material from two cases cited in this series showed organisms on culture.) "It would appear that bone cyst is a term which

should be restricted to the cavities in bones which contain fluid and have no definite connection with disease of the surrounding tissue" (Silver). Silver and Landon recognize three groups in the morphologic classification of intra-osseous bone lesions: (1) Infection; (2) metaplasia, and (3) neoplasm. To the first group belong the cysts arising from tuberculosis, syphilis, and osteomyelitis, which may be primary or secondary, single or diffuse; the type is usually recognized definitely from the history, clinical findings, and radiograph. The second group affords considerable difficulty in the establishment of the etiology, being either local or general and at times showing a tendency toward malignant change. They probably occur as a result of trauma, hemorrhage, metabolic disturbance, or systemic disease. The third group shades off from the almost benign giant-cell sarcoma to the very malignant sarcoma types, and will not be considered in this paper.

It would appear reasonable in the classification of the intra-osseous lesions to consider the clinical history and findings, and the radiographic, together with the pathologic, findings in determining the diagnosis. Elmslie in his second paper notes the lack of the clinical picture in previous literature and the preponderance of pathologic description and reviews of literature. It is with the hope of adding somewhat to the already rapidly accumulating data by presenting the clinical, laboratory, pathologic, radiographic, and surgical findings, and by abstracting the histories of the patients studied in the Mayo clinic, that this paper is presented.

*Local fibrocystic disease.*—Fibrocystic changes may be local or general and occur usually in the growing period of life. The proximal ends of the bones are principally involved and the tumor is unilocular or multilocular. The condition is most frequent in the femur, humerus, tibia, and fibula. In Silver's 97 cases the legs were involved in 57 and the arms in 40, 73 per cent being in the three largest bones, the femur, humerus, and tibia, in the ratio of 6:5:3. The symptoms vary, and in many instances a fracture is the first indication of a diseased condition in the long bone. However, usually there is pain, rheumatic or neuralgic in character, and a local swelling. In some cases there is tenderness, atrophy, deformity, shortening, or a limp complained of.

The diagnosis can be made only after a thorough clinical history, and physical and radiographic examinations have been made, and then cannot always be determined with certainty until an exploratory operation has been performed to rule out chondroma and giant-cell sarcoma, etc.,



by pathologic examination. The principal point to be determined is the question of malignancy, next the extent of bone involved, and whether the disease is truly a local process. Having this in mind, the surgery necessary in a given case may be arranged. The age incidence, slow growth, lack or character of pain, or the radiograph alone cannot always be depended on in making accurate diagnoses.

In the differential diagnosis it is necessary to consider sarcoma, chondroma, osteomyelitis, and syphilis, and, rarely, secondary carcinoma. Malignancy is the most important factor to be considered, as on this often depends the fate of the extremity. Giant-cell sarcomas are more often found extending from the diaphysis and involving the epiphyseal ends of the long bones. They seldom break through the cortex to invade the surrounding structure as the more malignant type are prone to do, rather remaining local and appearing more fibrocystic in character. It is impossible always to differentiate the sarcomatous group from osteitis fibrosa cystica by the radiogram alone.

Carcinoma of the bones, secondary to malignant growth elsewhere, is usually evident from the physical findings, the history, the characteristic radiographic appearance of the tumor formation, and the intense pain that usually accompanies it. The radiogram shows a moth-eaten, destructive appearing area. Fractures may occur and there may be a loss of normal bone striation, etc.

Syphilis is usually evident from the history and the physical or laboratory findings, and the radiograph often shows the periostitis and cortical thickening which are more or less characteristic, but it is not to be forgotten that syphilis may simulate almost any other lesion. The Wassermann test is not to be considered as final unless substantiated by other findings.

Osteomyelitis may simulate a cyst, and after considerable time may produce one containing fluid free from bacteria, called osteitis aluminosa. As a rule, there is an invasion of the surrounding structures, however, with a shading off from normal tissue into the cyst. Frequently there are inflammatory changes in the neighboring areas and a thickened cortex and periosteum, and, not infrequently, the presence of a sequestrum. The characteristic features of osteitis fibrosa cystica are: It usually appears before the patient is thirty years of age. It is always in the diaphysis and never invades the epiphysis. After slow growth it appears to move upward in the diaphysis and is most common in the proximal end of the shaft. If a single cyst, it arises from the center of

the bone usually, and slowly enlarges at the expense of the cancellous bone, leaving a clear line of demarcation. It causes no thickening of the periosteum and tends to grow away from rather than toward the epiphysis. There is little or no pain, but limp, deformity, or fracture, etc., frequently occurs. It would appear that the formation of a fibrous lining of the cyst was an index to its duration. Silver found it in a case at the second operation; he had noted its absence at the first. It might be likened to the condition found in chronic empyemas in which the wall of the cavity becomes an inch thick as a result of the chronic inflammatory process. If the cyst becomes multilocular, it presents a series of translucent areas surrounded by striæ of irregular outline known as trabeculations. The cortex being gradually encroached on becomes thin or fused with the medullary substance so that there are areas in which only the outline of the cortex can be made out. As the process continues the periosteum bulges out and becomes irregular, but in benign growths does not burst its bounds and invade the soft tissue, as is usual in the malignant growths. Later, the bone, having lost its normal structure, becomes weak and fractures on moderate trauma.

It is possible to diagnose some cases of osteitis fibrosa cystica from the radiograph alone; in others the gross and microscopic characteristics and the entire clinical picture or exploratory surgery must be resorted to in order to diagnose the condition. Too much value should not be placed on the radiographic appearance. Evidence of the invasion into the surrounding soft tissue by the extension of the tumor through the broken periosteum should make one think of malignancy. It is to be remembered that the benign growths cause pain by pressure on sensitive structures, nerves, etc., while acute infections cause pain, tenderness, local heat, and fever. Carcinoma, usually from a primary focus, has a typical radiographic picture, showing ill-defined outlines and marked destruction with moth-eaten appearance or the metastatic round areas of increased density and loss of striation.

#### TREATMENT

It has been demonstrated that osteitis fibrosa cystica may develop and after a period of growth may reach a period of rest, then gradually disappear or fracture and then heal. Fractures seem to unite in the greater number of cases with little or no callus-formation and may be often treated as simple fractures. The indications for operation are, therefore, not urgent unless there is interference with function, deformity,

patient was somewhat better, but the symptoms returned and she was referred to the Mayo Clinic.

*Examination.*—The child was well nourished. The right breast contained a small nodule and the cervical glands were shot-like. The left upper third of the humerus was enlarged and somewhat tender and there



Fig. 316.—Case 1 (63924). Bone graft in position after excision of the diseased bone.

was a slight restriction of the shoulder motion. The urine findings were negative. The radiogram showed a tumor of the upper half of the left humerus—probably an osteosarcoma.

*Operation, Feb. 13, 1912.*—Subperiosteal excision of the upper shaft and neck of the left humerus and a transplantation of a triangular piece of the tibia were done, the tibia being driven into the medulla of the

humerus a distance of one inch. The pathologist reported a bone cyst of the left humerus (Fig. 316). Six and one-half years after the operation the patient's physician wrote: "Though there is some shortening, there is good function and there are no signs of recurrence."

**CASE 2 (176139).**—F. P., a girl, aged seven years, was examined Oct. 24, 1916. She had had pneumonia, tonsillitis, and la grippe. The present complaint was pain and soreness, with a limp and a tumor the size of a lemon in the upper third of the left fibula. Without knowledge of trauma, the child had complained of pain, principally in the morning

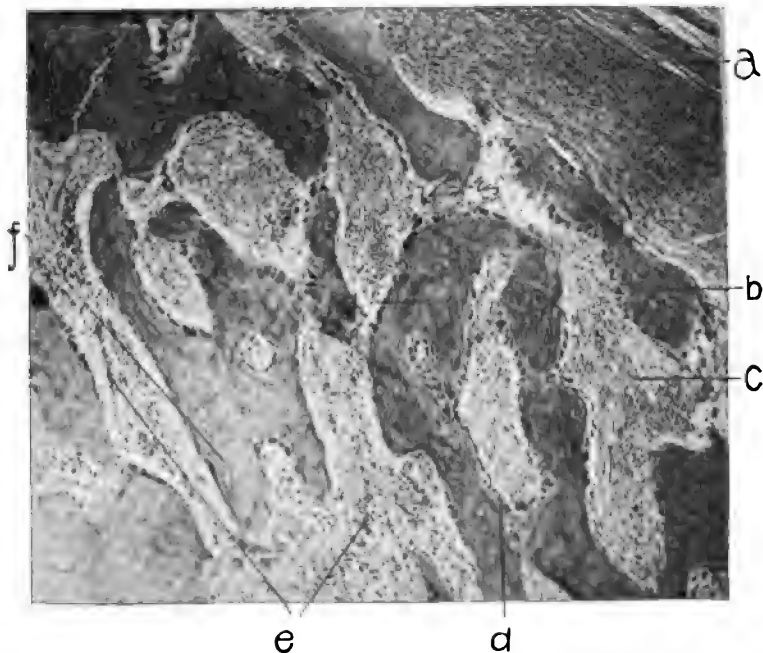


Fig. 317.—Case 2 (176139). Osteitis fibrosa cystica. Sections taken from the margin of diseased area. (Low power.) *a*, Very vascular periosteum; *b*, bone containing some cartilaginous cells; *c*, fibrosis; *d*, cells lining the bone margin, probably osteoclasts and osteoblasts; *e*, blood cells; *f*, cartilage cells.

and evening, in the upper third of the fibula some four months previously. The mother, on examination, had found some swelling and thought there was a little redness. During the last month there had been a decided aggravation of the limp.

**Examination.**—A tumor about two inches in diameter was noted in the upper third of the fibula. There was a slight enlargement of the superficial veins with a little tenderness and a shiny skin. The tonsils were enlarged and there were adenoids. The left leg measured 10½ inches and the right 9 inches in circumference. The examination other-

wise was negative. The urine findings were negative. The hemoglobin was 75 per cent. The leukocytes were 14,000; the polynuclear neutrophils, 52 per cent; small lymphocytes, 24 per cent; large lymphocytes, 18.3 per cent; eosinophils, 4.3 per cent; basophils, 7 per cent. The radiogram showed a tumor of the upper third of the diaphysis of the fibula not involving the epiphysis and fusing the cortex and medulla into a cystic cavity containing fine trabeculations. The epiphyseal line was distinct. The periosteum at the lower border was raised and the border of the tumor rough.

*Operation, Oct. 27, 1916.*—Subperiosteal excision of the upper third

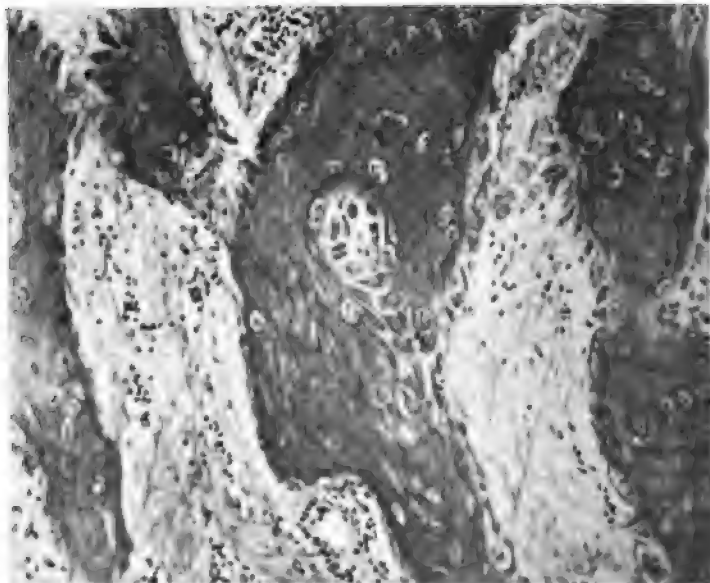


Fig. 318.—Case 2 (176139). Osteitis fibrosa cystica. (High power.)

of the left fibula and closure without drainage were done. The epiphysis was not removed. Pathologic report: Hemorrhagic bone cyst.

The cyst had probably been present a long time before the symptoms developed. Trauma may or may not have been a factor. The pain was only present when the child was not asleep or at play. The limp may have resulted from perineal nerve pressure. The case had been diagnosed as a sarcoma clinically because of the findings in the radiogram, and the apparent rapidity of growth, with enlarged veins, etc. The marked destruction of the fibula was a misleading feature. There were no complications following operation, and the child was discharged the ninth day, walking (Figs. 317, 318, and 319).

**CASE 3 (144401).**—N. D., a female, aged fifteen years, was examined Oct. 27, 1915. Four years previously the girl's teacher had noticed a deformity of the right wrist. There was no knowledge of previous trauma and no impairment of function. One year previously she had fallen off a wheelbarrow and thought her right thumb had been broken. For the past six months the wrist had been weak and painful.

*Examination.*—There was marked deformity at the wrist and limitation of motion in all directions, with crepitation on movement. The teeth were foul and the tonsils inflamed and very large; adenoids were present. There was tender-



Fig. 319.—Case 2 (176139). Osteitis fibrosa cystica of the left fibula in a girl aged seven years. The diaphysis only is involved. Cortex and medulla are fused into a cystic mass showing fine trabeculations. Operation: Subperiosteal excision of upper third of fibula. Pathologic report: Osteitis fibrosa cystica.



Fig. 320.—Case 3 (144401). Osteitis fibrosa cystica of the right radius with fracture. Cyst limited to the diaphysis. Operation: Bone graft used.

ness over the appendix and the temperature was 99. The urine showed albumin on two successive days. The Wassermann test was negative. The hemoglobin was 80 per cent, the red blood count was normal, and the white blood count 14,200 on two examinations. The radiogram showed destruction of the lower diaphysis, probably due to fibrocystic disease.

*Operation, Nov. 4, 1915.*—The lower two inches of the diaphysis of the right radius were excised and a bone graft transplanted from the

right humerus of a sharp, stabbing character, at irregular intervals. At the same time a dull pain was noticed in the palm of the right hand and in the fingers, which became worse when she was working. There was no acute infectious process and the temperature and general condition were good. The pain gradually became more severe until at the end of six months, when it became unbearable and consultation was sought. A radiogram showed diseased bone. An operation was done and a diagnosis of tuberculosis made. There was no pus until the second or third day. The drainage continued for a year and the symptoms were relieved for two years; they gradually returned, but were not so severe as before the operation. During the previous five years there

had been but little change; changes of weather and temperature aggravated the pain. Little local tenderness, heat, or definite fever was noted. Examination showed enlargement of the upper right humerus with some tenderness on firm pressure and a bony mass on the inner aspect, probably resulting from the previous operation, the scar of which was on the anterior surface of the arm. There were enlarged tonsils and adenoids, hypertrophic rhinitis, and a partly occluded left nostril. The urine showed a specific gravity of 1026, acid, and a small amount of albumin. Hemoglobin, 70 per cent. The radiogram showed osteitis fibrosa cystica (Fig. 323).

The patient was not operated on and four months later wrote stating that her condition was unchanged and that there was still some soreness in the palm and shoulder, and slight tenderness on pressure.



Fig. 324.—Case 6 (150574). Cyst of the left tibia. Communicating cysts found at operation. Recovery.

CASE 6 (150574).—V. J., a male, aged nineteen years, came for examination Jan. 22, 1916. The patient, a delivery clerk, had noticed pain in the left tibia off and on for the past four years. The pain was present mainly at night and was accompanied by swelling of varying degree. On one occasion the pain was of such severity that he was unable to work for a month and sleep was interfered with. Three days before examination at the Mayo Clinic pain and swelling appeared and subsided within forty-eight hours. There had been no discharge from the ankle. Examination showed an enlargement of the tibia just above the ankle, with a slight edema. There was no limitation of motion in the ankle. No note was made as to tenderness or local heat. The tem-

perature was 99. Rhinitis and pharyngitis were present and the tonsils contained pus and caseous material. The urine was negative. Hemoglobin was 80 per cent, and white blood count 10,600. The radiogram showed areas of decreased density in the lower end of the tibia, one large and the other small—the two evidently communicating. There was no evidence of inflammatory change about the bone nor was the periosteum altered.

*Operation Jan. 27, 1916.*—The cysts were found to communicate and to contain fluid. The wound was packed and healed quickly. Subsequent radiograms showed the cavity filling in with bone at the end of nine months, the patient having been entirely relieved.

*Diagnosis.*—Bone cyst of the lower end of the left tibia at the epiphyseal line, resulting from an inflammatory process, probably tuberculous (Fig. 324).

**CASE 7 (171941).**—L. J. L., a male, aged sixteen years, was examined Sept. 7, 1916. The boy had had tonsillitis and a tonsillectomy was performed nine years previously. For the past nine months he had had recurring attacks of severe pain in the right arm, without knowledge of trauma. The condition had been diagnosed as neuritis and later as bone cyst or sarcoma. Examination showed a well-developed boy. The right arm was slightly atrophied and a small, hard bony mass could be palpated at the right bicipital groove. The urine was normal. Hemoglobin, 88 per cent; white blood count, 9200. The Wassermann test was negative. The radiogram showed a cystic formation in the upper third of the right humerus, probably a subperiosteal hematoma which had ossified and formed a cavity.

*Operation Sept. 12, 1916.*—Through an incision passing longitudinally with the deltoid muscle a bony mass was exposed and chiseled into, liberating a red, serosanguineous material. The cavity, which was wholly in the cortex, was curetted and cauterized. Pathologic examination revealed a fibrous bone tumor containing a few giant-cells.

The bone cyst was probably of traumatic origin. The patient was discharged on the seventh day and has since been free from pain or recurrence. A radiogram taken six months later failed to show recurrence (Figs. 325 and 326).

**CASE 8 (86957).**—M. P., a female, aged twenty-five years, a school-teacher, who gave a history of having had erysipelas six years previously,

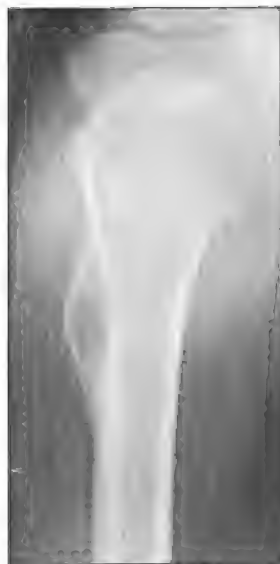


Fig. 325.—Case 7 (171941). Cyst of the cortex of the right humerus before operation, probably subperiosteal.



was examined July 1, 1913. Until five years previously she had walked normally; there had been no pain or weakness in the legs. About this time she had had a severe jar, but no discomfort until six months later when pain became noticeable running down the outer side of the right thigh and the hip seemed to catch when she attempted to run. Disability and discomfort gradually increased. She had been treated by osteopathy without benefit. While walking in the snow one day there was a sudden crack in the hip and she was unable to bear weight on the leg. She was taken to a hospital; it was believed that the hip was

fractured, and ether was given and the hip set. Weights were applied for six weeks, when roentgen and clinical examinations were made and tuberculosis and coxa vara diagnosed. Weights were again applied for three months, and massage given. Since then she had been about on crutches and had been generally healthy. The pain was most marked when the leg was used a great deal. On examination the right leg was one inch shorter than the left, and there was swelling of the calf. Abduction was limited but adduction was normal. There was pain on flexion. The patient held the right leg crossed over the left and used two crutches. Urinalysis showed 1020, acid, and albumin a trace. The hemoglobin was 80 per cent; white blood count, 8400; red blood count, 5,440,000. The Wassermann test was negative, the



Fig. 326.—Case 7 (171941). Right humerus six months after the removal of cyst.

blood-pressure was normal. The radiogram showed an old fracture with cyst-like formation in the greater trochanter.

*Operation July 4, 1913.*—A cyst at the head of the right femur was found. An ivory plug was driven through the greater trochanter into the neck of the right femur. One year later the right hip was injected with 2 per cent formalin and glycerin. Three and one-half years afterward the leg was much stronger, and the patient was able to get about on it. X-ray examination, August 3, 1915, showed the head of the femur in good position. There was apparently some cystic formation remaining. X-ray examination, July, 1916, showed no apparent

change. The patient walked with more comfort and there was less pain.

**CASE 9 (95333).**—Mrs. A. A., aged thirty years, was examined Nov. 12, 1913. Six years previous to examination the patient had had pain of a general character in the right leg, and at times in the hip, thigh, knee, ankle, etc., the pain coming on only when a sudden jar was sustained. Little attention was paid to the pain until two years previously, when it became worse and was more localized about the hip and knee. There were difficulty and stiffness in walking, but crutches or a cane had not been used. Massage had been given for four years.

*Examination.*—The right hip held stiff; motion limited in all directions; adductor spasm; one and one-half inch shortening, and the trochanter extended above Nélaton's line. The x-ray showed arthritis with coxa vara of the right hip and cystic degeneration of the head and neck of the femur.

**CASE 10 (219836).**—N. B., a boy, aged eight years, a farmer's son, was examined Jan. 23, 1918. Six months previously the boy was kicked in the hip by a cow. No pain followed, but he limped at times. While skiing about five months later he fell, and a physician declared the leg to be broken. He was taken to a hospital where the x-ray showed a diseased condition of the bone. A definite diagnosis was not made, sarcoma, tuberculosis, and cyst being considered. The examination at the Mayo Clinic showed enlargement of the left thigh, its circumference being 4 cm. greater than that of the right; there was no shortening. There was pain on deep pressure. The teeth were decayed, the tonsils enlarged, and enlarged cervical glands were present. The urinalysis was 1019, acid, with a few granular casts. The radiogram showed a large cyst of the left femur, probably hemorrhagic.

*Operation Jan. 31, 1918.*—The cortex of the left femur was so thin it could be cut with scissors. A large cavity from 4 to 5 inches in length and 1 to 1½ inches in diameter, filled with a serous, mahogany-colored fluid and some old blood-clots, was broken into. There was no distinct lining membrane. A diagnosis of osteitis fibrosa cystica was made.



Fig. 327.—Case 10 (219836). Left femur. Cystic degeneration (single). Medulla enlarged and cortex thinned. Trabeculations not typical of osteitis fibrosa, being heavier at the edge of the cyst and not running out into it; more like a rarefaction of bone from pressure, as in hemorrhage, etc. History of trauma about two years previously. At operation the cyst was found to contain a mahogany-colored fluid and a small blood-clot.

This patient is still under observation (March, 1918) and sections of tissue are being decalcified (Fig. 327).

**CASE 11 (115150).**—S. B., a female, aged sixteen years, came for examination Sept. 14, 1914, because of a swollen, painful right knee. She had had a peritonsillar abscess, otitis media, recurring attacks of tonsillitis, and diphtheria. Two years previously she had noted at irregular intervals sudden sharp pain in walking or climbing stairs. There was some limitation of motion in the joint, but no definite locking. Four months previously the knee became swollen and was treated with

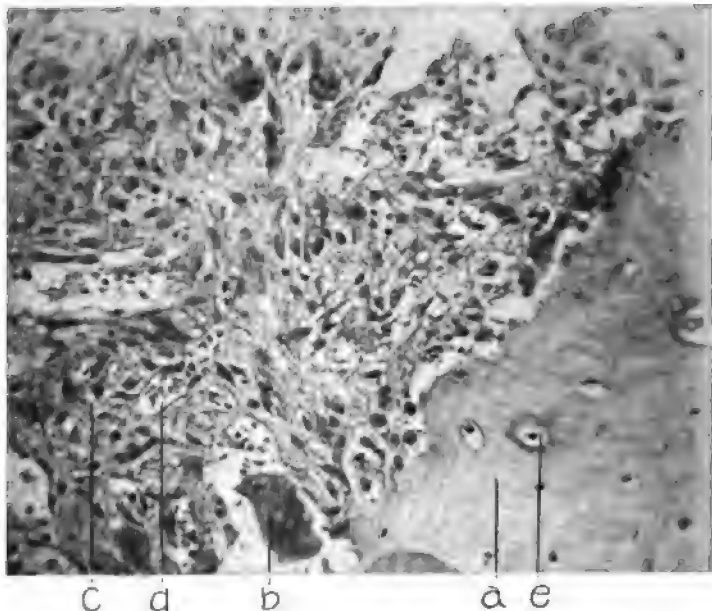


Fig. 328.—Case 11 (115150). Bone cyst of the right femur. Specimen taken from the thinned cortex. At operation the cavity was found filled with blood-tinged fluid and organized blood-clot. The wound was curetted and cauterized. Three years and three months later the patient was reported well without evidence of deformity or recurrence. *a*, Bone; *b*, giant-cell (one found in four slides examined); *c*, area of fibrosis; *d*, blood-vessel. (High power.)

iodin applications, etc., and a radiogram taken. She was advised to have the bone opened and curetted. About this time the knee was injured and she was confined to bed. The pain, particularly at night, was very severe. A diagnosis of sarcoma was made from the radiogram, and amputation at the hip-joint advised by a surgeon of international reputation after the knee-joint had been aspirated.

**Examination.**—The right knee was swollen and enlarged, the flexion limited to 30 degrees, but complete extension was allowed. There was a small scar at the upper end of the patella; little or no local heat. The circumference was  $1\frac{1}{2}$  inches greater than that of the left knee. The

knee was held in a somewhat flexed position and attempts to straighten it caused intense pain. The patient's general appearance was excellent. The temperature was  $99\frac{1}{2}$ . The urinalysis was negative; the hemoglobin 77 per cent, and leukocytes 13,000. The Wassermann test was negative. After a radiographic examination an exploration of cystic tumor of the lower end of the femur was advised.

*Operation Sept. 17, 1914.*—The tumor of the right femur was found to be filled with blood-tinged fluid. The cavities were curetted and cauterized, and the wound was closed without drainage. The pathologic

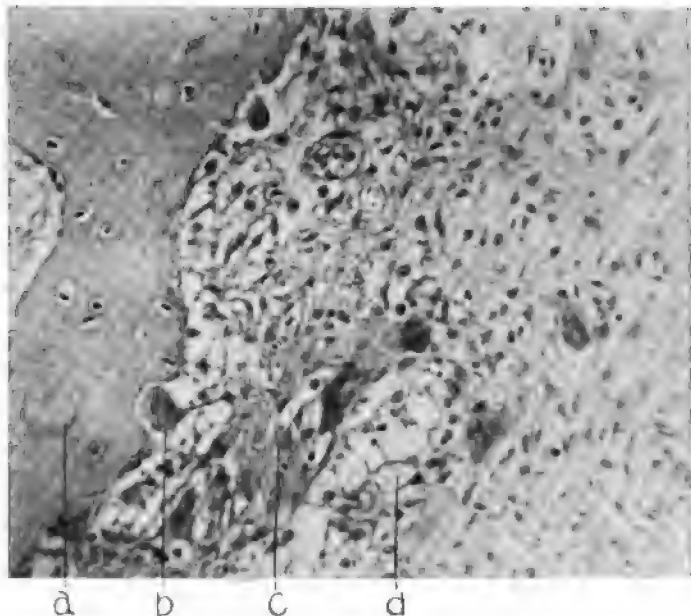
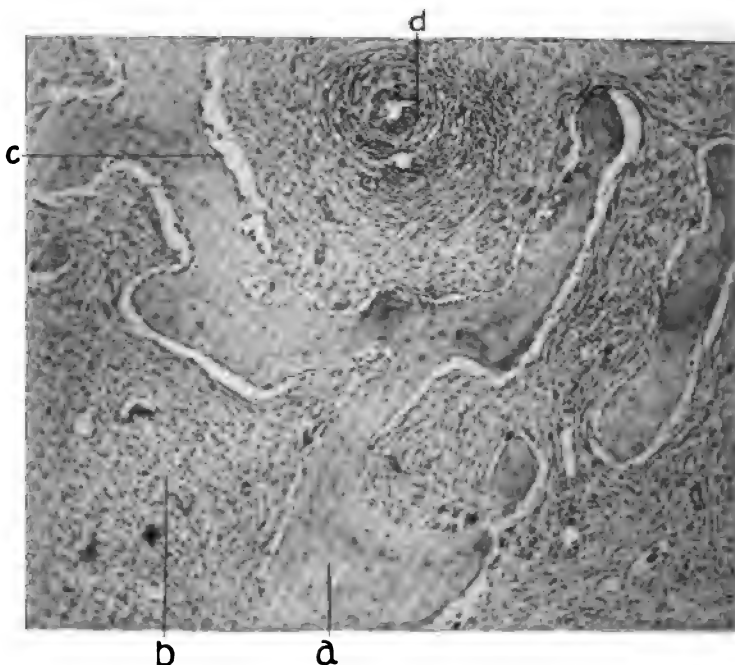


Fig. 329.—Case 11 (115150). See Figure 328. (Low power.)

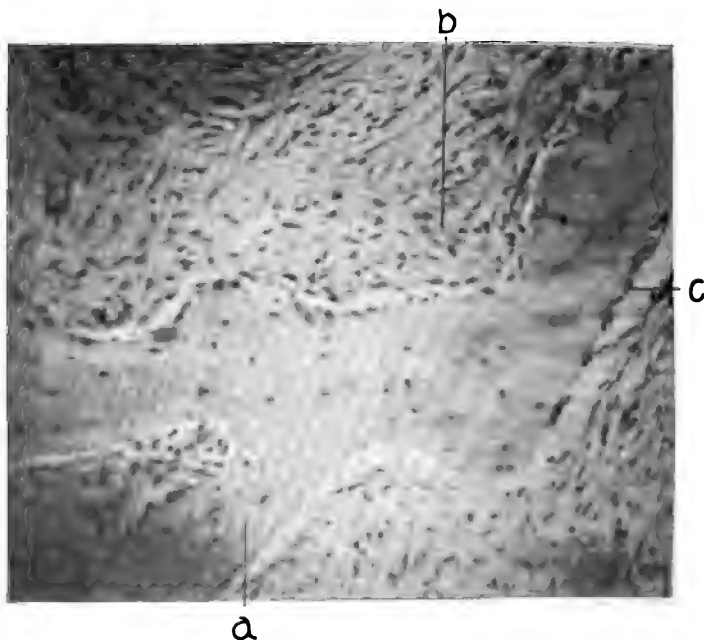
examination showed bone and organized blood-clot. There was no evidence of malignancy.

Sept. 15, 1915, one year after operation, the patient states that she is in perfect health, and there is no evidence of recurrence of the trouble (Figs. 328 and 329).

**CASE 12 (76480).**—M. G., a male, aged thirteen years, was examined Nov. 22, 1912. Four years previously, in throwing a stick, the patient thought he felt something snap in the right humerus. A physician examined the arm and assured him there was no serious trouble. Two years later the same accident occurred, and three weeks before examination he fell and injured the shoulder and since then there had been limitation of abduction.



**Fig. 330.**—Case 13 (115338). General osteitis fibrosa cystica. Bone trabeculae and the fibrous connective tissue lying between. (Low power.) *a*, Bone trabeculae; *b*, area of fibrosis; *c*, cells along border of bone, probably osteoclasts and osteoblasts; *d*, whorl of fibrous tissue about a blood-vessel.



**Fig. 331.**—Case 13 (115338). General osteitis fibrosa cystica. (High power.) *a*, Bone trabeculae; *b*, area of fibrosis; *c*, cells along border of bone, probably osteoclasts and osteoblasts.

*Examination.*—A hard, smooth, fusiform swelling in the upper third of the right humerus was found. The radiogram showed a cystic mass in the upper third of the right humerus, with evidence of fracture.

*Operation Nov. 25, 1912.*—The cyst was curetted and swabbed out with iodine. *Diagnosis:* Osteitis fibrosa cystica of the right humerus with old fracture.

Five weeks after the operation the patient reported that the tumor was becoming smaller and he was beginning to use the arm.



Fig. 332.—Case 13 (115338). General fibrocytic disease. Coxa vara, fracture of femur, and deformity. Thin cortex blending with medulla, the entire bone showing fine trabeculations.

CASE 13 (115338).—R. W., a male, aged seventeen years, was examined Sept. 16, 1914. A paternal aunt was epileptic and tuberculous. Five years previously the patient had noticed a slight stiffness in the left hip and had begun to limp and have occasional pain. Five months later he fell and fractured the left femur six inches above the knee; union resulted and he had no further trouble until seven months later when the same bone fractured two inches higher up. A radiogram taken at this

time showed the fracture, but nothing else was noted. Union was slow in taking place and it was nine months before he was able to bear full weight, and malunion occurred. Three more fractures occurred in the next four years, the patient presenting himself to the Mayo Clinic with a fracture in the upper third of the femur, of nine weeks' duration. Examination showed a marked outward bowing of the left femur, with  $3\frac{1}{4}$  inches of shortening, atrophy of the thigh and calf, and limitation of



Fig. 333.—Case 13 (115338). General fibrocystic disease. Femur below site of fracture shows cortex thicker but invaded at several points by cyst.

motion of the hip in abduction flexion. Flexion of the knee was limited to 90 degrees. The tonsils were enlarged and adenoids were present. The urine showed albumin on two examinations. The Wassermann test was negative. Hemoglobin, 87 per cent; red blood count, 5,480,000; leukocytes, 8100; polymorphonuclears, 56.7; small lymphocytes, 26.3; large lymphocytes, 13.0; eosinophils, 3.0; basophils, 1.0. On radiographic examination the right femur showed general fibrocystic disease, coxa vara, and old and recent fractures; the cortex and medulla were

fused in certain areas and showed fine trabeculations. Similar changes appeared in the right tibia and fibula. Other bones were negative.

*Operation Sept. 24, 1914.*—Excision of four inches of the upper half of the left femur and transplantation of bone graft. Pathologic examination revealed osteitis fibrosa cystica.

Eight months later the family physician wrote that union was firm, with 4 inches of shortening, and there was no further pain. It was a type of general osteitis fibrosa cystica, probably the von Recklinghausen type (Figs. 330-334).

CASE 14 (56898).—L. L., a female, aged twenty-one years, was examined Feb. 6, 1918: An appendicectomy had been done three years previously. Fifteen years previously the right radius was fractured and no further trouble was noted until eight years later, when a tumor formation was recognized in the same region and a physician was consulted, who advised operation; a specimen was removed for examination. A diagnosis of sarcoma was made and amputation advised but refused. Pain disappeared and improvement was shown until seven years previously, when the patient was brought to the Mayo Clinic and the tumor excised by removal of the upper three inches of the right radius. A diagnosis of giant-cell sarcoma was made. The arm recovered perfect function. Five years later a tumor developed in the right frontal region, and about four years later a small mass appeared in the right tibia. There was no pain and the general health was good. Examination showed a mass in the right frontal region one inch in diameter which felt cystic on firm pressure. There was slight enlargement in the right tibia and femur, and there was some heat over the enlarged portion of the tibia. The right ovary was enlarged. The tonsils were large and chronically inflamed. Urinalysis was negative seven years previously and at this examination. The Wassermann test was negative. Hemoglobin, 74 per cent; white blood-cells, 7800. Radiograms made seven years previously

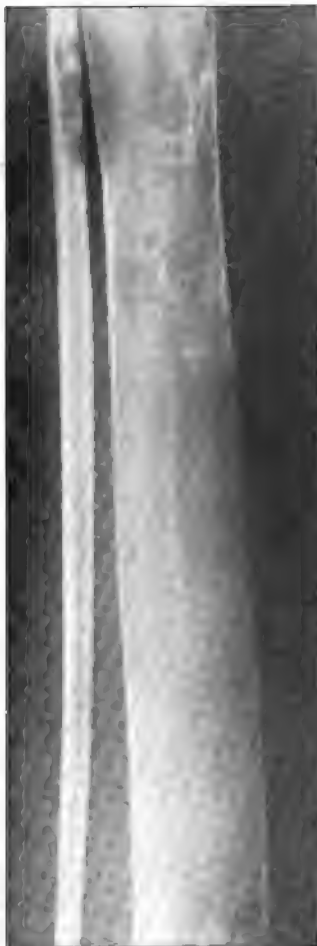


Fig. 334.—Case 13 (115338) General fibrocystic disease. Tibia and fibula. No line of demarcation between cortex and medulla in tibia and several well-defined cysts in fibula.



right fibula was fractured by a horse kick; in 1898 the right femur was fractured in a runaway, but healed in six weeks; in 1900 the left femur was fractured by tripping. His left leg was amputated on account of trouble (poor union) with the last fracture, rebroken. He still has a small sinus on the stump. He was anemic in appearance and afflicted with neuralgia.

G. W. (brother), aged thirty-two years. At the age of eleven years he slipped and fell, fracturing the right femur. Seventeen months later the left femur was fractured in falling from a horse; healed with good result. In 1905 he fell from a bicycle and fractured the left femur.

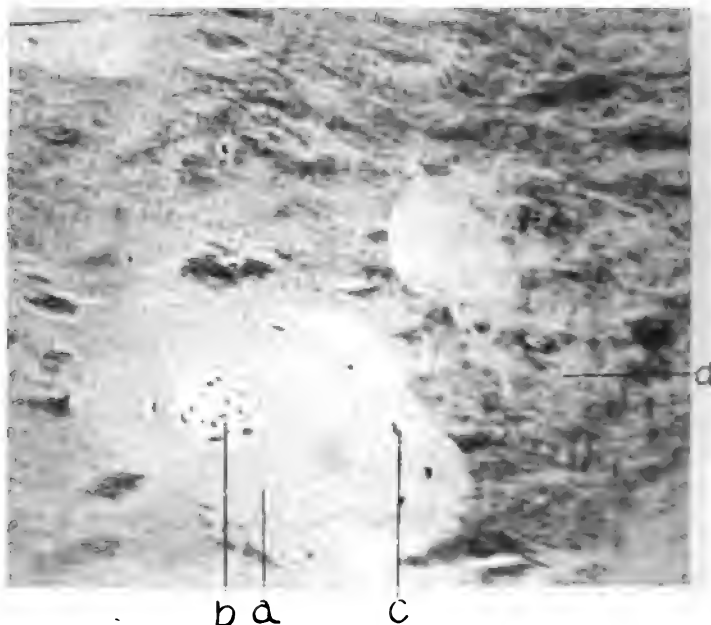


Fig. 340.—Case 15 (119482). General osteitis fibrosa cystica. *a*, Dense bone; *b*, blood-vessels, etc.; *c*, cartilage cell in bone; *d*, area of fibrosis.

There was bending at the site of fracture later. In 1907 the right forearm was broken; poor union.

Two brothers, aged twenty-two years and twenty-four years, were without fractures. T. W. (brother) had five fractures: In 1912, the right humerus; 1914, left femur; 1914, right femur; 1915, left femur; 1915, humerus.

D. W. (brother), aged twelve years. In 1911 the right femur was fractured; 1912, the right humerus; 1915, the left humerus; 1915, the right humerus; 1915, left femur.

J. R. W., Case 15 (119482), had three fractures; and J. G. W. had

two fractures; note Case 15 (119482) and Case 16 (119483). The total number of fractures in the family was twenty-three. The mother and three sisters were healthy. One sister had asthma and was anemic in appearance.

CASE 15 (119482).—J. R. W., a male, aged twenty-nine years, single, was examined Nov. 20, 1914. No venereal disease was admitted. At the age of ten years he sustained a fracture of the right humerus



Fig. 341.—Case 15 (119482). Right femur. Non-union for twelve years. Cystic disease with trabeculation of medullary cavity and thin cortex. Notwithstanding this malposition and non-union the patient was able to bear considerable weight on the leg.

which healed and gave no further trouble. When fourteen the left femur was fractured. Under splints, and, later, a cast, it healed in excellent position with good functional result. When seventeen years of age the right femur was fractured in a fall. A cast extending only a few inches above the site of fracture was applied and an attempt to walk the fifth week afterward disclosed non-union; malposition developed, which has persisted and required the use of crutches ever since.

Examination disclosed five-sixths of an inch shortening in the right leg, together with a pseudo-arthritis and considerable angulation of the fragments. General examination showed a man appearing somewhat older than his years; gray hair, fairly well developed and nourished: height, 5 feet, 2.5 inches; weight, 105 pounds. The urine was negative



Fig. 342.—Case 15 (119482). Left femur. Results of a fracture fifteen years before. Bone cysts numerous about site of fracture. Cortex is not thin; medullary cavity is somewhat filled in. Treatment: Splints and cast.

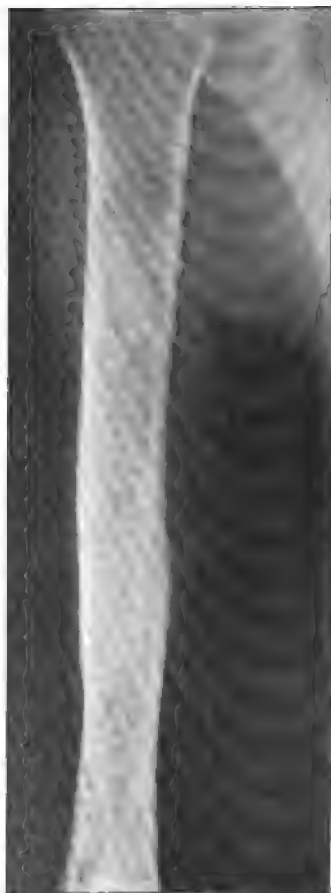


Fig. 343.—Case 15 (119482). Fracture of right humerus nineteen years previously. Old, perfectly healed fracture, multiple bone cysts, and thinning of cortical bone.

but for a trace of albumin. The systolic blood-pressure was 146; the diastolic, 80. Examination of the nose and throat showed enlarged tonsils, shaded antra, and atrophic rhinitis. Blood count showed hemoglobin, 87 per cent; erythrocytes, 5,100,000; leukocytes, 10,000; (300 cells counted); polynuclear neutrophils, 56.7; small lymphocytes, 27.7;

large lymphocytes, 9.3; eosinophils, 6.3. The Wassermann test was negative. Radiographic examination disclosed a fibrocystic degeneration of the long bones characterized by striæ and involving the medulla mostly, but sometimes encroaching on the cortex with slight or no change in the periosteum.

*Operation Jan. 28, 1915.*—The pseudo-arthritis was cut through, releasing fluid; the fibrous tissue was excised and a piece of bone from



Fig. 344.—Case 15 (119482). Tibia and fibula, showing cystic disease. Cortex and medullary cavity cystic, seem to have lost their characteristic radiographic features; fused in certain areas.

the upper fragment was removed. A Steinman peg was driven through the os calcis and an extension applied. Five weeks later bone was transplanted from the flat internal surface of the right tibia by the intramedullary method, and a Thomas extension splint applied. The wound healed by first intention. A month later a plaster-of-Paris cast was applied from the costal margin to the ankle. During the next six months temperature and pulse were normal and union slowly took place. Pathologic examination revealed osteitis fibrosa cystica.

Sept. 28, 1915, the general condition was good; there was a gain in weight, but the leg was weak and unable to bear weight. Aug. 20, 1917, the patient's brother wrote that the leg had healed "all right" (Figs. 340-346).

**CASE 16 (119483).**—J. G. W., a male, aged twenty-six years, was examined Nov. 20, 1914. He denied venereal infection. At the age of



Fig. 345.—Case 15 (119482). Radiogram after the insertion of a Steinman peg through the os calcis and the application of extension; fragments loosened and a part of the upper bone excised. Position improved and lengthening obtained. Taken five weeks after first operation.

twelve years the right humerus was fractured while he was throwing a stone. When nineteen years old he fell and sustained a fracture of the middle third of the left femur. The treatment consisted of a 12-pound Buck's extension for fifteen days, then of a plaster-of-Paris cast for seven weeks. He was allowed to walk at the end of six months but non-union was found and Buck's extension was again resorted to for two months, followed by splints, but no improvement was noted. Examination disclosed pseudo-arthritis and malposition of the middle third of the left femur with a 3-inch shortening. Radiograms of bones are shown in Figures 347-350. The patient appeared older than his years. The heart, lungs, and other organs were negative. Blood count: Hemoglobin, 88 per cent; erythrocytes, 4,-

520,000; leukocytes, 36.0; large lymphocytes, 6.0; eosinophils, 8.7; basophils, 2.0. The Wassermann test was negative. The urine showed a trace of albumin, but was otherwise negative.

**Operation** Nov. 27, 1914.—The ends of the bones were freed and traction obtained by Steinman's pegs from the os calcis and extension applied. On Feb. 4, 1915, a second operation was done. The fractured ends were exposed, one-half inch sawed off either end, and an intra-

medullary bone-plug, obtained from another patient, inserted and a Thomas splint applied. Two weeks later the Steinman plug was removed and the Thomas splint replaced. The wound had healed by first intention. There were no post-operative findings of any importance; the temperature as well as the pulse remained normal. Subsequent to operation there was three-fourths inch shortening. There was evidence of union of the bone graft on the upper end, but apparent failure in the



Fig. 346.—Case 15 (119482). Radiogram of skull, showing normal sella turcica. No evidence of cystic degeneration observed. Patient has plate in upper jaws.

lower end. In a letter from the patient Sept. 28, 1914, he stated that his general health was good and his weight had increased from 112 to 166 pounds, but that as yet the leg had not firmly united.

The patient returned to the Clinic in February, 1917, for further treatment. The general condition was good.

*Operation Feb. 21, 1917.*—A bone graft was taken from the left tibia and transplanted to the left femur for malunion. The patient was discharged May 5, 1917.

In a letter written Aug. 20, 1917, the patient states that the cast had been removed on the advice of the attending physician. The leg was very weak, the muscles swollen and hard, but there was no pain. The right leg was a little sore. Nov. 1, 1917, the leg was still weak and unable to bear weight in walking. The right leg was entirely healed. The patient's general condition was not so good as in the previous report (Figs. 347-350).



Fig. 347.—Case 16 (119483). Left femur, showing ununited fracture in malposition after seven years. Multiple cyst-formation. Pseudo-arthritis. Patient able to bear considerable weight.

**CASE 17 (41571).**—Mrs. W. H. N., aged thirty years, was examined June 18, 1915. The patient first came to the clinic in 1910 on account of goiter symptoms; the second occasion was in 1915, when she was again under observation because of exophthalmic goiter. She gave a history of having fractured the left humerus as a result of slipping; in attempting to save her from the fall her husband caught her by the hand, the slight trauma breaking the arm. A diagnosis of giant-cell tumor was made. Union was obtained by conservative measures.

Recent trauma had resulted in a thickening of the right humerus. No evident bone disease was discovered until a radiogram was taken following the fracture. A letter from the patient's family physician, May 24, 1915, gave the following report: "On April 29 she suffered a pathologic fracture of the humerus through a bone cyst. Osteitis fibrosa cystica was diagnosed. X-ray showed a similar but smaller area of diseased bone in the upper end of the radius. The fracture seems to be doing well." Examination showed, in addition to the goiter findings, enlargement of both humeri in the middle third. There



Fig. 348.—Case 16 (119483). Tibia and fibula showing longitudinal striae containing cysts. Involvement of both medullary cavity and cortex.



Fig. 349.—Case 16 (119483). Right humerus, showing healed fracture of upper third of fourteen years' standing. Few cysts.

was albumin in the urine; specific gravity, 1019. Radiographic examination showed cystic degeneration of both humeri—osteitis fibrosa cystica.

June 24, 1915, the patient was operated on for exophthalmic goiter (thyroidectomy). No operation was performed for the bone condition (Fig. 351).



CASE 18 (156552).—F. T., a male, aged nineteen years, a bank clerk, was examined April 4, 1916. He had noticed, since six years of age, a swelling over the fifth metacarpal bone of the right hand. There was no definite history of trauma. He had been told by his family physician that the finger was dislocated. No treatment was used, but the finger was pulled in an attempt to straighten out the dislocation which he thought present. Two months previous to coming to the Mayo Clinic an



Fig. 350.—Case 16 (119483). Cystic bone disease of left femur after operation. Was freshened and traction obtained by Steinman peg through os calcis.

x-ray was taken, a diagnosis of tumor was made, and operation advised. On admission the patient complained of weakness in the left hand, but had free use of all fingers. The tumor was enlarging slowly, but caused no pain unless traumatized. Examination showed a bony mass over the fifth metacarpal bone of the right hand. X-ray examination showed a cystic degeneration of the fifth metacarpal bone and second proximal phalanges of the fourth and fifth fingers. There was no pain and only slight tenderness on pressure. There was moderate hypertrophic

rhinitis, the tonsils were considerably enlarged and contained caseous material. The Wassermann test was negative. Urinalysis was negative.

*Operation April 14, 1916.*—The cyst walls were crushed, liberating a currant-red gelatinous material. Bacteriologic examination showed cultures on anaërobic agar of a facultative anaërobic diphtheroid bacillus. The patient was heard from six weeks later and was doing well (Fig. 352).

**CASE 19 (172169).**—Mrs. M. E. B., aged forty-one years, was examined Sept. 11, 1916. One sister and two brothers had died of tuberculosis. Three children were living and well, nineteen, eighteen, and fourteen years of age respectively. She had had grip and tonsillitis many times and gave a history of "neuralgia" off and on for fifteen years. She had always complained of being constipated. Previous operations were trachelorrhaphy, perineorrhaphy, and curettage ten years before. Fifteen years previously there had been a dull aching pain in the left forearm, diagnosed as "neuritis," which improved in a few weeks with treatment. Thirteen years previously there had been attacks of severe pain in the superior maxillary bone, with headaches, followed by malaise. Seven years previously pain developed in the outer side of the right thigh; it was treated as "neuritis," and disappeared in a few weeks with treatment, but was followed by a nervous breakdown. A

second nervous breakdown occurred five years previously, and one year later abdominal exploration was advised because of dull, persistent pain in the right side. The first recognized sign of bone trouble appeared in the upper tibiæ in 1913. In 1914 aching was noticed in the left ulna, and a lump appeared just above the wrist. The pain was of the same neurotic type as before, and later the neck, shoulder, and left side became involved. Operation was done January, 1915,

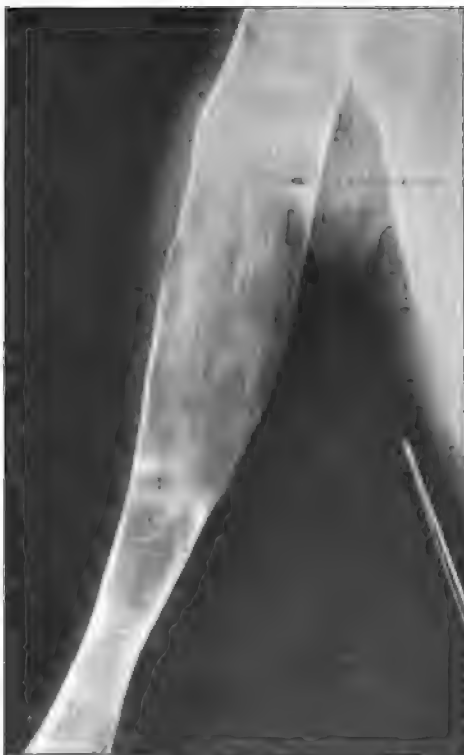


Fig. 351.—Case 17 (41571). General fibrocystic disease. Right humerus, showing fibrocystic change.

elsewhere. The left tibia was explored and a section taken, which was pronounced non-malignant. The intense pain subsided. The right tibia had been less painful than the left and seemed to improve of itself. Seven months previous to her coming to the clinic she was x-rayed and all the long bones were found to be cystic. She spent nine weeks in a hospital afterward and her condition became better generally under treatment.

*Examination* showed that the lower end of the left ulna was enlarged. There was moderate chronic rhinitis. The tonsils were enlarged but no



Fig. 352.—Case 18 (156552). Cystic degeneration in the hand. Cystic formation in the fifth metacarpal and the proximal and middle phalanges of the fourth and fifth fingers. The contents of the cysts were found to be jelly-like at operation.

pus demonstrated. The Wassermann test was negative. Examination of the blood showed hemoglobin, 80 per cent; leukocytes, 8600; erythrocytes, 4,880,000. Urinalysis showed acid reaction, a trace of albumin, and some pus-cells. Radiographic examination. There was cystic degeneration of the upper third of the tibia, lower third of the ulna, and both radii. A diagnosis of generalized fibrocystic degeneration of the long bones of the von Recklinghausen type was made. Exploration of the tumor of the left forearm with crushing together of the shell of bone was advised.

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## THE PERONEAL TENDON AS A TRANSPLANT\*

M. S. HENDERSON

In certain injuries to the hand, the tendons may be divided. The patient may not present himself for some months after the injury, and the surgeon is then confronted with a great gap to be bridged between the ends of the tendon. Fascia lata removed from the thigh has been used with some success to make up this deficiency. Occasionally the patellar ligament is accidentally divided and there is lack of extension power with the consequent "flop" knee.

In two cases, one in which the hand was involved, and the other the knee, we removed a large piece of the peroneus longus and used it as a free transplant. In the knee the result was all that could be desired; the operation on the hand is too recent to justify the drawing of conclusions; however, the wound healed by first intention. I have not seen in the literature any reference to the use of the peroneal tendon as a free transplant, and, even though it may have been used, because of the general lack of knowledge concerning it, the method is herewith reported. The tendon has an advantage for transplantation over the fascia lata, in that it is a true tendon, ready to take on function as soon as nourished in its new home. The removal of the tendon causes no inconvenience to the patient, and it is possible that full regeneration takes place.

About seven years ago I had an opportunity to observe the work of Sir Robert Jones, and since then I have operated in many cases of rigid flat-foot according to his method, that is, removing an inch or more of the peroneal tendons. No bad results or failure of regeneration of the tendons have followed. When a piece of the peroneus longus is removed, the peroneus brevis remains and is ample for function, even if the peroneus longus does not regenerate.

After the field where the tendon is to be used is prepared (the leg having been prepared previously), the knee is flexed and the leg is

\* Reprinted from the Jour. Am. Med. Assn., 1918, lxx, 1456-1457.

rotated inward. Two small incisions are used. The lower incision is made below and a little in front of the external malleolus, where the long peroneal tendon is divided just before it turns around the sole of the foot to be inserted into the head of the first metatarsal bone. The upper incision is made just behind the fibula, about 3 inches above the tip of

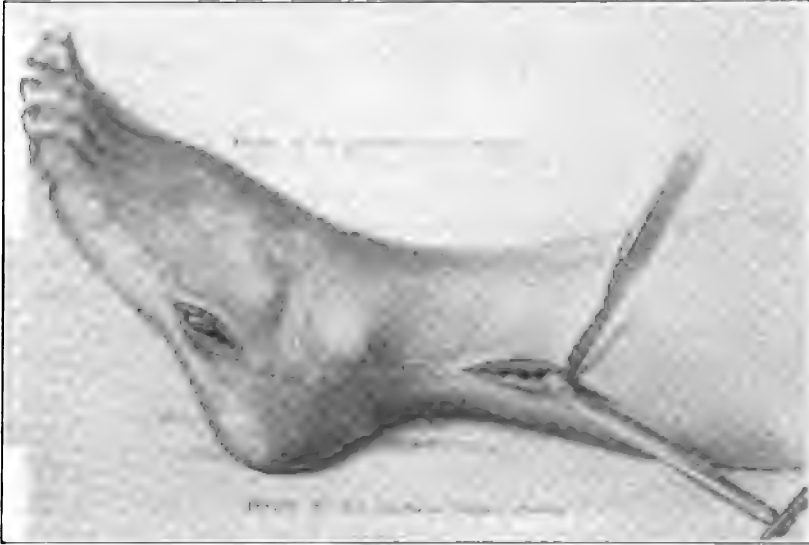


Fig. 353.—Method of removing peroneal tendon for transplantation.

the external malleolus, and the tendons are exposed. Pulling on the tendons above permits the peroneus longus to be readily identified; it is then divided below, and pulled up through the upper incision and divided there. In this manner 5 or 6 inches of large tendon may be obtained and divided longitudinally into two or three pieces if so desired.

# DERANGEMENTS OF THE SEMILUNAR CARTILAGES OF THE KNEE-JOINT\*

M. S. HENDERSON

The semilunar cartilages are the most common cause of mechanical derangement of the knee-joint, the internal being the chief offender.

The knee is a large hinge joint, and, placed as the two semilunar cartilages are between the long bones making up the joint, they are especially liable to injury. The internal meniscus is crescent-shaped, whereas the external makes nearly a complete circle. They are both wedge-shaped, their bases being toward the periphery of the joint. They aid in deepening the depressions for the articular surfaces of the condyles to rest on the tibia. The external cartilage has no very strong attachment to the capsule of the joint and is thus permitted a certain amount of motion, which allows it to glide out of harm's way when threatened with being caught between the joint surfaces. The internal meniscus, on the other hand, has, along the peripheral border, a firm attachment to the capsule. Its close association with the anterior and inner part of the capsule, into which a few fibers of the quadriceps are inserted, undoubtedly is occasionally responsible for the disturbance of the normal contour of the cartilage, and, on extension of the knee, the nipping of the cartilage between the joint surfaces.

## SYMPTOMS AND PATHOLOGY

The symptoms produced by mechanical derangements of these menisci are explainable only by the pathologic condition present, and in a discussion of the subject they should be considered together.

It is rather strange that derangement of the semilunar cartilages has received so little attention in America. This has been commented on by various English authorities, to whom we must turn for most of our information on the subject. Unquestionably, mechanical derangement

\* Presented before the Minnesota State Medical Association, Duluth, August 28-30, 1918. Reprinted from *Minn. Med.*, 1919, ii, 133-142.

of the cartilages is less frequent in the United States than in England. The English youths and young men play "soccer" football, which, next to coal-mining, is the most common source of the trouble. In America soccer is almost unknown, and our football, similar to the English Rugby, is not played so universally. Moreover, the character of play is not so apt to cause injury to the knees as is soccer. American surgeons are greatly indebted to Sir Robert Jones for his articles, which have occasionally appeared in our journals. He has done more than any one else to awaken our interest in this subject. Sir Rutherford Morison and Martin, both at Newcastle-on-Tyne, have reported large series of cases. In that region the miners work in seams which are so low that they are forced to keep their knees flexed, and naturally, in order to maintain their equilibrium, they evert the feet—the position most favorable for injury to the internal semilunars. There is little doubt that we in America are not recognizing the condition as we should, and that many persons are going about suffering from this curable surgical condition.

The position favorable for the infliction of injury to the internal semilunar cartilage is partial flexion of the knee and eversion and outward rotation of the foot, so as to rotate the head of the tibia outward on the femur. With the knee in this position the internal semilunar cartilage is placed deeper in the joint than it is in any other position. If the rotating force is applied above instead of below the knee, with the knee partially flexed, but with the foot in the normal position, the femur will rotate inward on the tibia, and the same condition in the knee will be present; that is, the internal cartilage will be nearer the inner part of the joint. If in this position the knee is extended, the smooth surface of the inner condyle of the femur may roll down and catch the inner semilunar cartilage. This movement, brought about by the action of the powerful quadriceps while the person is working or participating in some game, is usually quick and sharp, and cannot be checked in time to prevent damage to the cartilage. The cartilage must either slip away, be torn, or crushed. The external cartilage, if it happens to be caught, as I have mentioned, has considerable mobility and may escape. The internal cartilage is closely bound to the capsule and is not permitted this latitude of movement. The type of injury sustained by the meniscus depends on the point at which the crushing force is inflicted on it. If only the anterior end of the cartilage is caught, it may be torn loose, and this portion may hang as a more or less pedunculated loose body. The chief symptom produced by such a cartilage is recurrent locking.



Owing to the fibrous character of the cartilage, it must be extremely rare for a complete transverse tear to be produced and a free body formed.

If the condyle crushes the cartilage further back, the damage to the cartilage may consist of a longitudinal tear in the middle three-fifths, leaving the anterior and posterior fifths intact. The surgeon, in operating in such cases, when opening, as he usually does, over the anterior inner portion of the joint, may be deceived when he sees the anterior end apparently intact. The middle three-fifths of the meniscus in this type of case usually lies in the middle of the joint, that is, the torn portion lies to the outer side of the internal condyle in the intercondylar notch. This has been referred to by Morison\* as a "bucket handle" fracture. The outstanding and typical symptom of such pathologic findings is, in not a few instances, a persistent lack of complete extension. In this type the typical attacks of recurrent locking may also occur.

When the patient is seen immediately after the accident, there are pain and disability, and effusion soon appears. The locking may still be present, and an attempt at reduction should be made at once. Place the patient on a hard bed, a table, or on the floor. Flex the knee fully with the muscles relaxed, rotate the tibia inward, and then forcibly and rapidly extend the limb, the surgeon pressing on the knee. Usually it can be reduced in this manner, but if the attempt is not successful, it may mean that the middle three-fifths of the cartilage lies caught in the intercondylar notch. Full flexion of the knee preceding the extension may release such a torn bucket-handle cartilage, but if this fails there is nothing to do but to open the joint and remove the cartilage. If reduction is successful, the knee should be kept in a cast or splint for at least four weeks to permit the cartilage to grow in place. Although the surgeon may apparently obtain full extension, if the patient insists that "things do not seem right in the joint," it is wise carefully to consider such a statement by the patient, and not to be too confident that reduction is complete.

More often the patients come to us after many lockings, each attack having been followed by pain and swelling. Some weeks or months may intervene between the accident and the second locking. The patient usually volunteers the information that walking on rough ground or

\* This type of fracture was described in a previous article by the author.<sup>2</sup> He was not aware at the time of the very descriptive nomenclature applied to it by Sir Rutherford Morison.

stubbing the toe with the knee partially bent and the foot turned outward is the position in which the locking or catching occurs. The story may not be clearly told, and it is only by careful inquiry that a diagnosis can be made. The patient may be able to release the cartilage by certain motions, the disability may be of only a few minutes' duration, and the soreness following negligible. Many persons go through life with a loose cartilage producing slight symptoms without seeking surgical aid. If the locking is more complete and painful, there is no sudden feeling of release; marked swelling and disability ensue, and the patient is laid up for some days. The pain and tenderness, as a rule, are located over the anterior extremity of the cartilage, although many patients complain of the pain being diffuse and mostly under the patella. If the pain is located on the outer side of the joint, it usually means that the external cartilage is involved. Sir Robert Jones calls attention to the fact that he has rarely known pain from the internal cartilage to be referred to the outer side. Sir Arbuthnot Lane and Sir Robert Jones both call attention to the occasional development of tuberculosis of the knee in patients who have previously presented symptoms of a loose semilunar cartilage. They accordingly urge that the operation shall not be deferred in well-marked cases. Most certainly, in a few patients suffering with tuberculosis of the knee, a very clear history, extending over many years, of typical locking of the joint may be elicited. The observation is interesting because intermittent chronic irritation with subsequent inflammation is generally recognized as an etiologic factor in the production of cancer, but not of tuberculosis.

#### DIFFERENTIAL DIAGNOSIS

The radiogram is an aid in the diagnosis only in so far as it is of negative value. Rarely does a semilunar cartilage cast a shadow on the plate, and then only if it is doubled up and greatly thickened, owing to the repeated traumas inflicted on it. Every knee presenting symptoms of mechanical derangement should be rayed, as this is the only way to differentiate in some cases between a loose osteocartilaginous body and a loose semilunar body. The loose osteocartilaginous body, due to osteochondritis dissecans, or osteochondromatosis, casts a definite shadow.

In the case of a loose osteocartilaginous body there is often, but not necessarily, a history of direct trauma followed by pain. The desiccation of the body occurs later, and it may be only after some weeks that locking is present, whereas in the case of a loose semilunar cartilage

the injury is indirect, followed by pain with immediate locking. As a rule, the effusion, and in fact all the symptoms, are less marked in the cases of loose bodies than in the semilunar cases.

A certain group of patients complain of a sort of slipping, not really a catching or locking. No effusion or disability follows, and the pain is not severe. Such cases are not surgical, and it is possible the symptoms are produced because a little fat synovial tag is being nipped occasionally between the joint surfaces.

It is always well to question the patient as to whether or not he ever feels anything "come out." By that term he often means a protuberance to be felt on the inner side of the knee, over the anterior extremity of the internal semilunar cartilage. This may be present when the knee is "out of joint." If what the patient feels always presents itself in the same place, at the anterior inner part of the knee, it is probably a semilunar cartilage, but if it presents itself at one time above the patella in the suprapatellar pouch, and at another on the inner or outer side, it is probably a loose osteocartilaginous body.

In another group of cases there is a complaint of semi-catching or slipping suggestive of a loose cartilage, but usually the patient is middle aged and there is no definite history of trauma. One must be on guard not to mistake the onset of a hypertrophic arthritis for a mechanical derangement. The points that should be fulfilled before a diagnosis of deranged internal semilunar cartilage is made are: (1) A history of injury to the knee not necessarily direct; (2) pain, disability, and locking of the joint, followed by effusion, and (3) a negative radiographic examination. Once the diagnosis of damaged semilunar cartilage is made the treatment must be surgical—either non-operative or operative. If the patient is seen at the time of the accident, the treatment should be immediate reduction as herein outlined, followed by fixation in a cast or splint for four weeks. Only occasionally will it be necessary to open the joint in a recent case. A safe general rule to follow is that a knee having had but one derangement should not be opened. The technic for the removal of the internal semilunar cartilage which has been found satisfactory in the Orthopedic Section of the Mayo Clinic is, briefly, as follows:

#### TREATMENT

The day previous to the operation the knee is carefully shaved and scrubbed with soap and water. This is followed by an alcohol rub and an alcohol dressing is applied and left on until time for the final preparation.

The anesthetized patient is placed on the table so that the knees come just over the split which allows the foot-piece to drop. The knee is prepared by the benzine and iodine method, care being taken that the scrubbing with benzine is done with the knee extended and flexed. In this manner the folds in the skin, both anterior and posterior, will be thoroughly cleaned. The leg is painted with iodine from the ankle to well up on the thigh. After the draping with sterile sheets and towels is completed, a tourniquet is applied to the thigh. The foot of the table is then dropped, and the patient placed in slight Trendelenburg position. The incision is started from opposite the middle of the patella to the inner side, coursing down a little in front of the condylar line, that can be plainly felt beneath the finger. The skin incision should be carried well down over the joint-line, curving it a little posteriorly, so that the shape resembles somewhat a hockey stick. The knife and tissue forceps that have been used are now discarded, and replaced by clean ones for the deeper work. Skin towels are carefully placed, so that sutures, etc., may not come in contact with the skin. The fascia and fat are incised and the joint opened. Blunt retractors may be placed within the joint to permit a view of the cartilage. If it is torn at the anterior end, the anterior two-thirds of the meniscus should be removed. It is seldom necessary to remove more than the anterior four-fifths of the cartilage—three-fifths is usually sufficient. Care should be taken not to divide the internal lateral ligament. In the removal of the cartilage from its attachment to the capsule in the region of the internal lateral ligament a little rim of cartilage may be left on the capsule, and thus any injury to the fibers of the ligament will be avoided.

After the removal of the meniscus the wound is closed layer by layer, using plain catgut, interrupted sutures. The skin is closed with silk-worm and horse-hair. A fairly heavy cotton dressing is put on firmly, and the tourniquet removed. A plaster-of-Paris cast is applied and worn for seven days. Gentle motion is permitted as soon as the cast is off. All the stitches are out by the twelfth day, and walking is permitted as soon as the patient wishes. If effusion ensues, an elastic bandage is worn for a time.

#### DISCUSSION OF CASES

As a basis for this study the records of 98 consecutive patients operated on in the Mayo Clinic have been examined. There were 18 patients between the ages of eleven and twenty years; 42 between

twenty-one and thirty; 20 between thirty-one and forty; 15 between forty-one and fifty; and 3 between fifty-one and sixty. Sixty were under thirty years of age. Seventy-seven were males and 21 were females. The right knee was affected in 44 instances, and the left in 54. The internal semilunar was removed in 94 instances and the external in 4.

In the selected cases which present typical symptoms in which the diagnosis has been carefully worked up the surgeon will usually find a torn cartilage either at the anterior end or in the middle three-fifths. It has been my usual custom to have placed on the surgical record whether or not the pathologic condition found seemed sufficient to account for the patient's symptoms. In a number of instances (18), although there was a more or less clear-cut history of locking, with the typical train of symptoms, the cartilage, at operation, appeared normal except for a little too much mobility involving the capsule in that area. Nevertheless the cartilage was removed.

This group of 18 cases is of interest, containing as it does evidently the poor selections for operation. It is stated by Mr. Fagge that there must be pathologic evidence, consisting of a tear (or fracture)\* of the meniscus before it is removed. In 4 of these 18 cases the results were excellent, and in 4 the results were generally satisfactory in that practically all the symptoms were relieved. It is undoubtedly true that so-called loose cartilages causing symptoms are rare, compared to the torn cartilage, but undoubtedly they occasionally do exist. The pathologic condition present in patients of this group who have responded favorably to the operation is, I believe, a laxity of the capsule, which, under certain conditions, permits of a catching of the cartilage between the joint surfaces. The pain may be extreme until the cartilage is released. In 3 of the group of 18 patients the results are unknown. In 7 the results were unsatisfactory, and it must be acknowledged that the diagnosis was wrong, or our search for the pathologic condition at the time of the operation was insufficient. None of the patients are worse.

In 9 instances the semilunar was removed in persons operated on for free osteocartilaginous bodies. This was done in our earlier cases, and in some, at least, was probably not necessary. The results, however, were all excellent.

In 13 instances the histories were insufficient to permit of any classi-

\* While the word "fractured" cartilage is used commonly, the term "ripped" or "torn" is in reality more descriptive of the pathologic condition present. The semilunar cartilages are fibrocartilaginous in structure and rarely fracture but do commonly rip or tear in their longitudinal axis.

fication as to the type of injury to the cartilage, but the results were satisfactory in 9 and unsatisfactory in 4, showing that the paucity in the notes, at least in some cases, was probably due to paucity in the pathologic condition.

In 58 cases of the series a torn and misplaced cartilage was found. The notes in some of these did not show the exact location of the tear, but in 21 it was definitely stated that the middle three-fifths was torn longitudinally, separated from the capsule, and lying in the intercondylar notch. This is the bucket-handle type of fracture so aptly named by Sir Rutherford Morison. The results in this group were excellent. It is more than probable that in some of our early cases in which the surgical notes were merely of misplaced or loose cartilage the condition was in reality torn cartilage.

I have limited my discussion to the internal semilunar cartilage, but the same technic applies to the external cartilage, except that the incision must be made, naturally, on the outer side, and once the joint is entered and the cartilage found to be at fault, its removal is not difficult, as the attachments to the capsule are not so firm as those found on the inner side. It is probable that the internal semilunar is damaged more than twenty-five times as often as the external. In our series four external cartilages were removed, but the symptoms were relieved in three only.

#### CONCLUSIONS

1. A semilunar cartilage should not be molested unless there has been more than one attack of locking.

2. The term loose cartilage is not correct. A ripped or torn internal semilunar will be found in the majority of cases. There is no uniform type of tear, but there are two common types, namely, the middle three-fifths, torn longitudinally and placed in the intercondylar notch, the "bucket-handle" tear, and the anterior extremity torn longitudinally and hanging as a loosely attached body readily nipped between the joint surfaces.

3. The symptoms which should be present are: History of trauma, usually indirect, pain, disability, locking of the joint, effusion, and a negative radiogram.

4. In atypical cases operation should be done only after very careful consideration.

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# OSTEOCARTILAGINOUS JOINT BODIES\*

M. S. HENDERSON

Osteocartilaginous joint bodies,<sup>3</sup> although of intrinsic origin, are in reality foreign bodies and inflict mechanical derangement and a certain degree of traumatic arthritis. The method of their formation is the most interesting phase of the subject. The present discussion is based on a study of 120 cases observed in the Orthopedic Section of the Mayo Clinic. The treatment has been wholly surgical, and we have removed such bodies from the knee, the elbow, the shoulder, and from the bursæ about the knee. The etiology, the symptoms, and the treatment will be considered in the order named, and the differences as seen in the various joints involved will be pointed out.

## ETIOLOGY

1. *Trauma*.—It is possible that a piece of the joint may be knocked off by direct trauma, thus causing a loose body. In our experience this has been a rare occurrence and will be referred to a little more fully under osteochondritis dissecans. Mr. Turner believes that we underestimate the relative frequency with which this happens. It may be, since Mr. Turner's work in such cases is chiefly among the coal-miners in the region of Newcastle-on-Tyne, that direct trauma is more often sustained by his patients. Our cases are drawn mostly from agricultural areas, and, comparatively speaking, direct trauma to the knee is much less frequent. Strictly, therefore, loose osteocartilaginous bodies produced in this manner would be in reality fractures. The knee is the only joint susceptible, as the shoulder, elbow, and other large joints are well protected by the surrounding muscles.

2. *Osteochondritis dissecans*.—We have never recognized this condition in any joints except the knee. It has long been recognized that there is a definite group of persons who are prone to develop loose bodies in the knee. Koenig first described the condition and gave it the name of osteochondritis dissecans. In America Freiberg and Wooley

\* This paper was compiled from articles listed under reference number 3.



and Ridlon first called attention to it. In a few instances I have seen it in both knees. For some reason desiccation of an area takes place generally on the internal condyle, a little to the inner side and just adjacent to the point at which the posterior crucial ligament is inserted (Fig. 354). Koenig's theory was that the end artery supplying this area became plugged, and in consequence the part was undernourished and sloughed off. In one instance only in our series of cases was the desiccated piece known to come from the external condyle. I have never known the tibia or the patella to be the site. While it is true that the



Fig. 354 (97040).—Osteochondritis dissecans. Loose body arising from the internal condyle resting in the spot of its origin.

presence of the body is brought to the attention of the patient and is often attributed by him to injury or trauma, such injury or trauma will often be found on careful inquiry to be due to nothing out of the ordinary, for example, a quick turn on arising from the sitting or squatting position. If, on the other hand, the trauma is more severe, such as results from falling on the flexed knee, on a stone, or a sharp edge striking directly on the inner condyle of the femur, the conviction may very readily be entertained that the loose body was produced by devitalization of the cartilaginous surface, with desiccation immediately or at some later time. In cases in which trivial indirect trauma is given as

the cause we must recognize the presence of a pathologic brittleness of the joint surfaces. The number of loose bodies produced in this way rarely exceeds two or three, and careful inspection of the radiograph will usually disclose the source as a flattened area on the internal condyle. While we have definitely recognized such a condition in the knee only, there is no reason why the elbow or shoulder should not be similarly affected.

3. *Hypertrophic arthritis*.—The marginal osteophytic growths associated with hypertrophic arthritis, occurring usually in elderly persons,



Fig. 355 (188030).—Loose bodies due to osteophytic growths of hypertrophic arthritis.

may break off and wander as small free bodies in a joint. Nourished by the joint fluid, they may attain large size. We have found this frequently to be the etiologic factor in the knee (Fig. 355) and elbow. It appeared to be the cause in the one case in our series in which the shoulder was involved, although the patient was young.

4. *Osteochondromatosis*.—In both the knee (Fig. 356) and the elbow (Fig. 357) we have encountered loose bodies in great number which could not be accounted for by any of the causes mentioned. When these joints are opened, the picture presented is unusual—a synovitis with inflamed lining, somewhat thickened and pedunculated into teats. These

irregular intervals, associated with pain and perhaps effusion, followed by a period of relief depending on whether or not the body finds a resting-place that prevents it from being caught between the articular surfaces. If it lies in the suprapatellar pouch, in the posterior compartment, or even in the intercondylar space, locking will not occur. It is only when it slips out of these places and glides into the anterior compartment that it produces symptoms. The locking, which is both irregular and uncertain, produces sudden disability and pain, which may be very severe and cause the patient to seek relief. As a rule, however, the locking produced by a loose body is apt to be transitory or momentary, with comparatively slight effusion, pain, and stiffness following; the opposite may be true when the semilunar is the offender. The patient is usually able, at some time, to locate a loose body in the knee, although the position varies, whereas with the derangement due to a semilunar, the protuberance of the cartilage, if there is any, always occurs at the same spot, namely, the joint line of the anterior and interior surfaces along the internal lateral ligament.

The treatment is entirely surgical. Often a single loose body, or even more than one, may readily be removed from the suprapatellar pouch under a local anesthetic. The knee is carefully prepared, the skin and subcutaneous structures are anesthetized, and the loose body carefully palpated and held between the fingers. A sharp cutting needle is thrust through the skin directly into the body, thus fixing it securely. With a sharp knife the dissection is carefully carried down to the body and it is removed. After this simple procedure the patient may be permitted to walk the same day. When the body is situated in the middle of the joint, as definitely ascertained by the radiograph, usually in a notch or a depression in the internal condyle, the inner condylar incision, used in the removal of the internal semilunar cartilage, may be employed. If, however, exploration of the entire anterior compartment is necessary, the patella should be split longitudinally, the fibers of the patellar ligament divided, and the fibers of the quadriceps split as far as may be desired above the patella. If there are loose bodies in the posterior compartment, some of them may be forced through into the anterior section. This is not always possible, and it may be necessary later to enter the posterior compartment by a posterior incision. It has not been our custom to do this at the primary operation, but preferably about two or three weeks later, and in the mean time not to allow any motion of the knee. The posterior approach is not easy, particularly if

the patient is fat or very muscular. The incision is six inches in length, running down the middle of the popliteal space. It is preferable to dissect down between the heads of the gastrocnemii so as to keep the nerves and vessels to the outer side. The popliteal muscle is dissected through, the ligament of Winslow is divided, and the joint entered. By slightly flexing the knee the capsule is a little relaxed and curved forceps may be introduced. If the bodies cannot be removed in this way, it may be necessary to force them out by palpation both within and without the wound. It is not always easy to remove them all. Following operation on the knee for the removal of loose bodies, if the incision is on the outer or inner side of the patella or on the posterior surface, a plaster-of-Paris cast should be worn for one week, but if the patella is split, a cast should be worn for from eighteen to twenty-one days.

### THE ELBOW-JOINT

It is not generally recognized that mechanical derangement of the elbow-joint is occasionally produced by the presence of osteocartilaginous loose bodies. A locking or impediment to motion in the elbow does not cause the same degree of inconvenience and suffering that a like condition would cause in the knee-joint. This fact, and the infrequency with which loose bodies occur in the elbow as compared with the knee, accounts for the general lack of knowledge concerning their presence in the elbow. Loose bodies in the elbow-joint may be classified into two groups:

1. Pieces of joint surfaces that have been knocked off in fractures. Such fragments are definitely due to trauma; they are often quite large and have to be removed in order that function may be reestablished. The condition will not be considered in this article.
2. Bodies not definitely due to trauma, found in numbers varying from one to twenty or more.

We have observed 14 patients with loose osteocartilaginous joint bodies. The right elbow was involved in 10, the left in 3, and both elbows in one. All the patients were males. Ten were operated on, and the number of bodies removed in each case varied from 1 to 65.

The etiologic status in each case is not as readily determined as in the knee-joint cases, because at the time of operation it is not possible to obtain such a good view of the joint surfaces of the elbow. In this series there has been no one case that we could definitely assign to the osteochondritis dissecans group. In the majority of cases, as nearly as

we could determine, the condition was due to the breaking off of osteophytic growths of a hypertrophic arthritis and in some to a definite osteochondromatosis. Rehn has reported loose bodies in the elbow-joint, but most articles on the subject of loose bodies refer to the knee-joint. Von Bergmann, in speaking of loose bodies in the elbow, stated that in his opinion free bodies are referable to an injury happening in youth. It is a fact that in some of our cases there was a history of severe trauma to the elbow years before that may have had a bearing on their formation. In others there was absolutely no history of injury. Trauma cannot be accepted as the direct cause of the bodies, but that it is undoubtedly a factor cannot be denied. The joint surfaces of the elbow are not subject to direct trauma, though indirect trauma, due to muscular violence, is at times undoubtedly inflicted. Some of our patients' first symptoms arose after unusual exertion, such as throwing a baseball, but that such action produced the loose bodies is doubtful. It is more probable that attention was at such times first drawn to the elbow by the locking or catching due to the body which was already there.

The symptoms are variable, depending on the amount of mechanical interference which the bodies cause to the action of the joint. The elbow-joint is a true hinge-joint, and restriction of motion in such cases is more common than locking, whereas the opposite is true of the knee-joint when it contains loose bodies. Some of our patients complained of limitation of motion—a little catching, perhaps, but no distinct locking of the joint. Others had definite locking, released by manipulation and accompanied by severe pain. All had some limitation of motion. Occasionally the joint locks while the patient is asleep, and he is aroused by the pain. There is often a certain resemblance to a tuberculous history, and the wasting of the muscles is absent. The radiograph establishes the diagnosis beyond question.

The condition should be treated surgically. The character of the joint and the importance of the surrounding structures occasionally make it difficult to remove all the bodies. If they are considerable in number, it will be found that the majority lie in front and to the inner side over the ulnar area. On the anterior aspect this is the safest approach to the joint.

#### OPERATION

The incision is made to the inner side of the biceps tendon, and usually it is necessary to divide the median basilic veins. The ulnar

nerve is behind the condyle and well out of harm's way. The median nerve and the vessels are to the outer side. The incision is carried down, the pronator radii teres fibers are separated, and, later, the brachialis anticus fibers are spread. The joint-capsule is exposed and opened. By flexing the elbow to about 45 degrees, a curved forceps may be introduced and the bodies forced out. If this procedure is not successful, the gloved finger may be introduced into the joint and the bodies palpated. Various maneuvers and manipulations may be used, such as palpating with the other hand while the opening into the joint



Fig. 358 (238014).—Osteocartilaginous loose bodies in the right shoulder-joint.

is held apart, and pressing on the joint from the outside, thus forcing the bodies out through the opening in the capsule. If the bodies are posterior in the olecranon fossa, the incision should be made through the lower fibers of the triceps. If the bodies to be removed are on the radial side, the incision is made to the outer side of the biceps tendon. The fibers of the supinator longus must be divided, great care being taken not to injure the musculospiral, the posterior interosseous, or the radial nerves. Any one of these incisions may suffice, or it may be necessary to employ two or even all three of them. Exceptional care must be taken to make the operation aseptic.

### THE BURSÆ ABOUT THE KNEE

Two patients in our series, both more than fifty years of age, who were operated on had osteocartilaginous loose bodies in the bursæ about the knee. The etiology in these cases was doubtful. They might be classified under osteochondromatosis. The symptoms were practically nil except for an occasional soreness and stiffness of the knee. Operation was advised because it was thought the disability might be caused by the bodies.

### THE SHOULDER

One patient had multiple loose bodies in the shoulder (Fig. 358). Inasmuch as there was but one such case, our symptomatology rests on

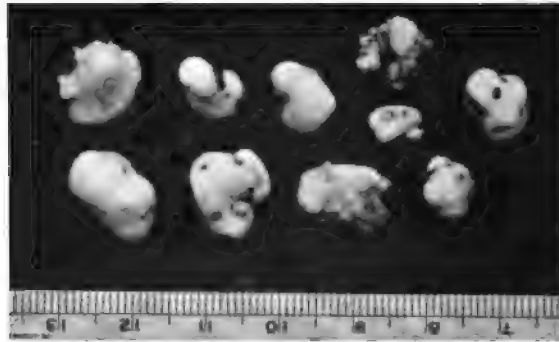


Fig. 359 (238014).—Ten osteocartilaginous loose bodies removed from the right shoulder-joint.

that alone. The locking is quite transitory, and is followed by pain and soreness. The locking or catching may be so frequent that the patient hesitates to use the arm, and the deltoid may be considerably atrophied, but such atrophy by no means reaches the degree seen in tuberculosis or definite arthritis. The treatment is removal of the bodies—the site of the incision is selected to suit the individual case. In our case a posterior incision was used on account of the thinness of the capsule in that area, and the bodies, ten in number, were manipulated around to the opening and removed (Fig. 359).

### CONCLUSIONS

Our entire series comprises 122 patients; in two of these the loose bodies were in the bursæ about the knee. The knee was by far the most

common site, the elbow next, the bursæ next, and the shoulder last. If any treatment at all is demanded, it is essentially surgical, and the relief depends on the thoroughness with which the bodies can be removed and whether or not they are the sole cause of the symptoms.

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## NERVES



# THE NERVOUS SYMPTOMS IN PERNICIOUS ANEMIA—AN ANALYSIS OF 150 CASES\*

H. W. WOLTMANN

It was not without some hesitancy that I selected this particular topic, since the literature on the subject is already voluminous, and additional contributions would almost seem unwarranted. A careful review of the subject, however, reveals that many of our pet views concerning pernicious anemia rest on a foundation that is indeed insecure; that there is existing the widest divergence of opinions, some of which may possibly be brought into harmony by facts that may be gleaned from the analysis of a larger number of cases; and that fundamental problems are still left entirely unexplained, the inherent perplexities of which greatly augment our desire to aid in their solution.

"The mind occasionally wanders," said Addison, when, in 1855, he gave to the world his classic description of idiopathic pernicious anemia. This statement practically summed up what was known of the central nervous system in its relation to pernicious anemia until 1886, when Lichtheim described three cases of the condition, which presented symptoms ordinarily seen in tabes. Although Lichtenstern, two years prior to this, had published an article entitled "Progressive pernicious anemia in tabetics," in which he considered the pernicious anemia to be dependent on the tabes, it was Lichtheim who first recognized the true significance of this syndrome.

The resemblance of these cases, both clinical and particularly anatomic, to tabes dorsalis is, however, only superficial. The changes in the cord have been longest known and studied in great detail. Here the degeneration is seen to begin as small, isolated plaques, with primary involvement, as a rule, of the posterior columns, later of the lateral columns also. These plaques, by confluence and secondary degeneration, ultimately bring about a diffuse and extensive disintegration of the

\* Presented before the Minnesota State Medical Association, August, 1918, Duluth, Minn. Reprinted from *Am. Jour. Med. Sci.*, 1919, clvii, 400-409. Copyright, Lea and Febiger, Philadelphia.

tremor. Another exhibited such marked choreiform movements that she would repeatedly drop objects, and fed herself only with great difficulty. In one instance a hemiplegic attack of three days' duration was seen.

In relation to the cranial nerves, diminution in the senses of smell, taste, and hearing was noted. A central scotoma gave one patient great inconvenience. Disturbances of taste are not infrequent: to one patient everything tasted sour; to another, bitter, and a third, with normal mentality, included in her dietary egg-shells and soft stones, which she carefully selected. Symptoms referable to disturbance of the eighth nerve, especially roaring, ringing, or thumping in the ears, are very common. Sometimes there is a distressing dizziness, and now and then fainting spells are noted.

As to the relationship between the time of onset of the disease, dating this from the first characteristic symptom and the time of onset of the nervous symptoms, there is nothing constant whatsoever. Thus a patient may die of pernicious anemia without ever presenting any evidence of central nervous system involvement; on the other hand, the appearance of nervous symptoms may antedate the onset of the anemia, as pointed out by Nonne and Bastianelli. This was true in 1.4 per cent of our cases, the symptoms that preceded being usually the paresthesias. In one case the patient had to resort to the use of crutches and catheterization before any anemia was apparent. The longest time interval noted was thirteen months. The duration of the anemia also showed no definite relationship to the time of onset in the nervous symptoms, though in the cases examined the mean duration of the anemia was 2.2 years, and the mean onset of the nervous symptoms ten and one-half months later.

TABLE 1.—NEUROLOGIC DIAGNOSIS BASED ON THE EXAMINATION OF 150 CASES OF PERNICIOUS ANEMIA, IN 80.6 PER CENT OF WHICH THE CENTRAL NERVOUS SYSTEM SHOWED INVOLVEMENT

Subacute combined sclerosis type of lesion . . . . .	99.2	per cent
Posterior sclerosis . . . . .	52.2	" "
Combined sclerosis . . . . .	45.4	" "
Lateral sclerosis . . . . .	0.8	" "
Multiple peripheral neuritis also present . . . . .	4.9	" "
Transverse myelitis with primary optic atrophy . . . . .	0.8	" "

A glance at Table 1 makes it at once apparent that the type of lesion par excellence of the nervous system as evidenced clinically is a subacute combined degeneration of the cord, regardless of whether this begins in

the posterior or the lateral columns or in both simultaneously, though the columns of Goll and Burdach are in the majority of cases first and most extensively involved.

Primary optic atrophy was seen but once, and, as Collier has emphasized, does not form a part of the picture. Why it should be present in this particular case is difficult to say. Collier has called attention to the possibility of lues being a factor in these cases. This assumption may be supported here by the finding of a transverse myelitis also, which is certainly uncommon in pernicious anemia, though by no means impossible, yet all other evidence pointing to this complication was lacking.

Of considerable interest is the finding of multiple neuritis, which could be demonstrated in addition to the spinal cord lesion in 4.9 per cent of the cases. Why a multiple neuritis is not found more frequently at necropsy is a fact rather difficult to bring into harmony with clinical experience, for, as this series shows, a neuritis is not so uncommon. In the vast majority of autopsied cases reported, however, the peripheral nerves were either not studied or no mention was made of them. I have been able to find but two cases in the literature in which degeneration was demonstrated in the peripheral nerves at necropsy. Von Noorden reports a case with parenchymatous degeneration in the N. tibialis and N. peroneus, and Eisenlohr in the N. saphenus dexter. Doubtless careful studies of necropsy material in selected cases would reveal neuritic processes to be more common than seems now to be the case.

While it is obviously impossible to submit detailed reports of all these cases, Table 2 represents, in brief, the nervous findings noted in their examination. The various headings have been arranged in order of their importance from a diagnostic standpoint, rather than in a sequence which would otherwise be more logical.

The cardinal findings anent the objective evidence pointing to involvement of the nervous system occur in the realm of sensation. Superficial sensibility was found to be definitely impaired in 42.4 per cent of the cases, excluding those in which the diminution was so slight as to be uncertain (Fig. 360\*).

As Figures 360 and 361 illustrate, it varied considerably in degree

\* The numerals used in the figures represent degrees of diminution or increase on a scale of four, 0 being normal, -4 signifying complete absence, +4 very marked increase. Numerals placed next to the figure and not otherwise explained refer to the condition of the reflexes. The stippling indicates diminution in superficial sensibility. Other findings not charted are normal.

and was usually most marked over the legs and the buttocks, there being no evidence of dissociation of touch, pain, or temperature, such as is seen, for example, in tabes (Fig. 361).

TABLE 2.—RÉSUMÉ OF FINDINGS IN 121 CASES OF PERNICIOUS ANEMIA WITH COINCIDENT INVOLVEMENT OF THE NERVOUS SYSTEM

SENSIBILITY		DEMINISHED		ABSENT					
Superficial (tactile, pain, thermal) . . . . .		42.4 per cent							
Deep									
Joint (toes) . . . . .		60.0		20.0					
Tendon . . . . .		12.8		0.8					
Vibration (256V) . . . . .		82.4		33.6					
Vibration or joint impaired . . . . .		92.0		..					
FUNDUS									
Pathologic . . . . .				63.4					
Low-grade retinitis . . . . .				33.0					
Hemorrhagic retinitis . . . . .				29.6					
Primary optic atrophy . . . . .				0.8					
MENTALITY									
Apathy and somnolence . . . . .				28.0					
Irritability . . . . .				9.6					
Memory defects . . . . .				7.2					
Dementia . . . . .				2.4					
Emotional instability . . . . .				3.2					
Depression . . . . .				3.2					
Psychosis . . . . .				0.8					
Total . . . . .				35.2					
REFLEXES		INCREASED		DEMINISHED		ABSENT		UNEQUAL	
Patellar . . . . .		39.2		28.8		7.2		14.4	
Either patellar or tendo Achillis . . . . .						24.8		21.6	
Tendo Achillis . . . . .		23.2		46.4		20.8		11.2	
Ankle-clonus (sustained) . . . . .		4.8		..		..		..	
Babinski positive . . . . .		26.4		..		..		..	
Oppenheim . . . . .		7.0		..		..		..	
Chaddock . . . . .		2.4		..		..		..	
Rossolimo . . . . .		1.6		..		..		..	
Mendel-Bechterew . . . . .		0.8		..		..		..	
COORDINATION								IMPAIRED	
Arms . . . . .								15.2	
Legs . . . . .								55.2	
ROMBERGISM . . . . .								52.0	
GAIT									
Ataxia . . . . .								28.8	
Spasticity . . . . .								4.8	
Spastic-ataxic . . . . .								8.0	
URINARY CONTROL						PARTIAL		COMPLETE	
Incontinence . . . . .						8.0		0.8	
Retention . . . . .						4.0		0.8	
MUSCLES				INCREASED		DEMINISHED			
Tonus (legs) . . . . .				16.0		10.4			
Power, disproportionately impaired, in legs . . . . .						8.0			
Complete paraplegia . . . . .						1.6			
Atrophy, localized with fibrillation . . . . .						0.8			
Choreiform movements . . . . .						0.8			

More significant still is the disturbance of deep sensibility, particularly of vibration and of joint sensibility, which, either singly or combined, were definitely impaired in 92 per cent. Here too the disturbance is, as a rule, limited to the legs, pelvis, and lower portion of the spine, the upper portion of the body usually escaping intact. It is a rather striking feature that vibration is more frequently and more markedly disturbed than joint sensibility, albeit both forms of sensation are supposed to travel up the cord in fibers which occupy relatively the

Diagnosis - Pernicious Anemia  
Subacute Combined Sclerosis

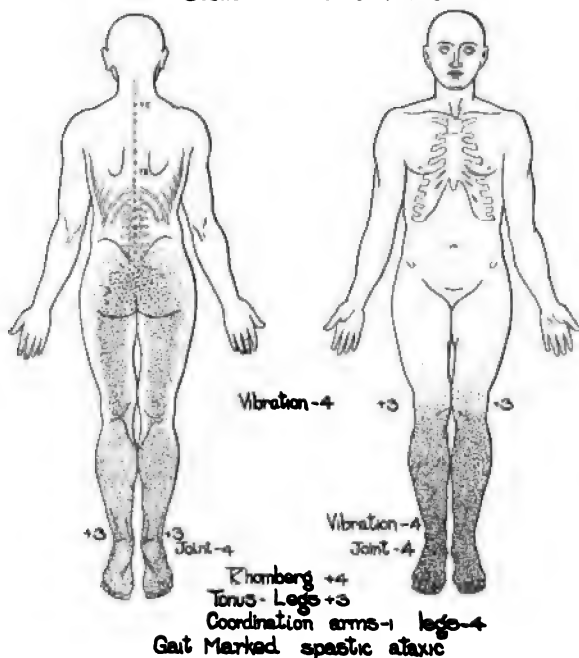


Fig. 360.

same position in the posterior column. This was very marked in some cases, complete absence of vibration sensibility, or pallesthesia, over the pelvis and legs being noted in 4.8 per cent, where joint sense in the toes was normal. The reverse was never observed to this extent, although in a number of instances joint sensibility was moderately impaired where pallesthesia was normal. The disturbance in deep sensibility is thus seen to be the most outstanding feature in the entire neurologic examination. In only 2.4 per cent of cases was the distur-



Diagnosis: Pernicious Anemia.  
Subacute Combined Sclerosis

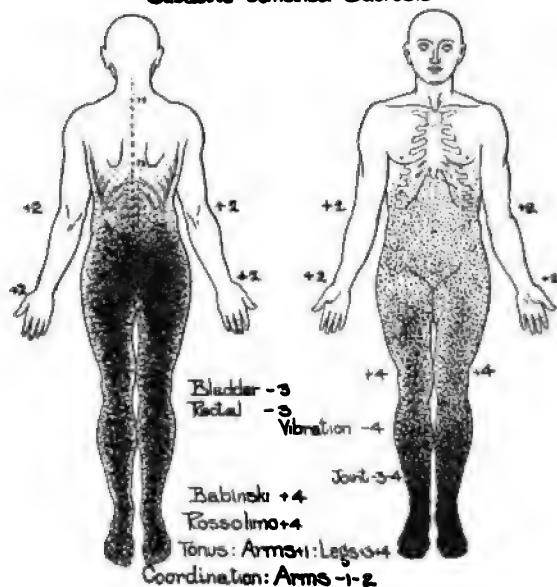


Fig. 361.

Diagnosis: Pernicious Anemia.  
Posterior Sclerosis

Subacute Combined Sclerosis

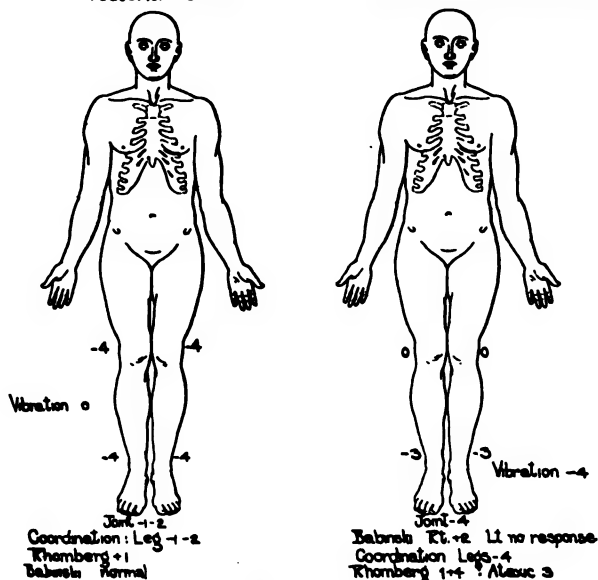


Fig. 362.—Same as Figs. 360 and 361. On the left, the findings when first seen; on the right, one year and ten months later. Although the knee-jerks have returned to normal, due to secondary involvement of the pyramidal tracts, other findings indicate that the degeneration of the spinal cord has progressed, and that in spite of a much more satisfactory blood-picture.

bance in superficial sensibility more marked than the diminution in deep sensibility (Fig. 362).

Within the past few years the psychic phenomena noted in these patients have been exhaustively studied, and numerous contributions have appeared, many of them interesting and scholarly, although the texts in psychiatry, on the whole, dismiss the subject with a few remarks or neglect it entirely. A more careful search into the mental condition of these patients would reveal a higher percentage of abnormality than is indicated in Table 2, in which only the outstanding features are noted. In only one case was there an outright psychosis present, and this was of the infection-exhaustion type. Here the anemia was ushered in with an acute hallucinatory confusion, which cleared up after three weeks, and reappeared once subsequently, *pari passu* with an aggravation of the patient's physical condition. A number of writers, among them Langdon, recognize in the psychosis something more or less characteristic, so that a diagnosis of prepernicious anemia has been made in the absence of anemia, which subsequent development of the case confirmed. The majority, however, consider these cases as belonging to the exhaustion type of psychosis, lacking any features which are especially characteristic. Psychoses of the better defined types, such as manic-depressive insanity, are looked upon as merely coincident, and have, *per se*, little or nothing to do with the existence of the pernicious anemia.

Relative to the condition of the reflexes, little need be added save in explanation of the chart. The absence of either patellar or tendo Achillis reflexes on one or both sides was noted in 24.8 per cent, and their inequality in 21.6 per cent.

In but one case was there noted a progressive paralysis, with atrophy and fibrillary tremors of the anterior tibial group of muscles on one side, which must be interpreted as a degeneration going on in the anterior horn cells. Doubtless this occurs, though not with the frequency maintained by Rothmann and Teichmüller, nor yet with the rarity claimed by some of their opponents.

The development of marked choreiform movements in this connection has not, as far as I have been able to learn, been reported before, and is of considerable significance in connection with the pathologic alterations noted in the cerebrum.

Some fourteen years ago a writer on this subject declared that "the study of the spinal cord in pernicious anemia had become an old story." This may be true. The fact remains, however, that our patients still

die, and while it may be a long time before any material advance is made in the knowledge of pernicious anemia, our satisfaction with the present status must not act as a shibboleth, preventing a better understanding of this disease.

Although the present paper adds little to the knowledge of the condition, I merely wish to emphasize the importance of a correct and early diagnosis in these cases, the prominence which nervous symptoms assume in this disease, and the aid which the examination of the nervous system, considering it as a diagnostic measure, may be to the internist.

### SUMMARY

The salient points of the knowledge gained by clinical evidence of the relation which the nervous system bears to pernicious anemia may be briefly summarized:

In 80.6 per cent of moderately advanced cases of pernicious anemia there is indisputable evidence of nervous tissue disintegration. This is in satisfactory accord with the pathologic findings, of which we may take the figures of Minnich, who demonstrated lesions in the spinal cords of approximately 77 per cent of cases of pernicious anemia.

Subjectively, some form of paresthesia, such as numbness and tingling, is rarely missing.

Objectively, one finds the most striking disturbance in the pathologically altered reflexes, not forgetting the tendo Achillis and Babinski reflexes, and the disturbance of vibration and joint sensibilities, the former of which may readily be tested with almost any type of tuning-fork.

As an adjunct in differentiating pernicious anemia from other anemias, the examination of the nervous system will be found of inestimable value; it often forms an easy way out of a most perplexing situation.

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# THE SURGICAL TREATMENT OF PROGRESSIVE ULNAR PARALYSIS\*

A. W. ADSON

Progressive ulnar paralysis is a clinical condition which has long been recognized, but has rarely been treated surgically. It has been diagnosed as a progressive muscular atrophy and as a form of muscular dystrophy. A number of patients have been examined in the Mayo Clinic who have had a single progressive ulnar paralysis and no other form of paralysis or atrophy. The operative findings in these cases verified the clinical condition and presented a marked interstitial neuritis, with a diffuse thickening of the nerve as well as nodular masses like neuromas.

*Symptomatology.*—The patients who have been under observation in the Mayo Clinic presented similar symptomatology: First, the complaint of various forms of slow, progressive sensory changes, such as paresthesias and anesthetics, that is, tingling, hypersensitive areas of the skin, and numbness along the course of the ulnar nerve. Second, trophic disturbances, atrophy of the small muscles of the hands, of the flexor carpi ulnaris, and of part of the flexor profundus digitorum which are supplied by the ulnar nerve; the atrophy of the hand is most prominent in the hypothenar region, and there is marked depression between the base of the thumb and the second metacarpal bone. Third, a progressive motor paralysis, first noticed as a definite weakness, and then a gradual loss of motor control of the muscles involved. This phase also presents a peculiar contracted condition of the two outer fingers (Fig. 363).

Recently we have operated on the ulnar nerve in three cases in which there were very definite pathologic findings. The nerve was found to be very much enlarged and to present one or more so-called "neuromas" (intraneural fibrous tissue). The enlargement was of the fusiform type, with definite thickening and hardening of the nerve itself, and the neuromas were quite definitely circumscribed, though

\* Presented for publication April 10, 1918. Reprinted from Minn. Med., 1918, i, 455-460.

more or less diffuse throughout the nerve tissue. The ulnar groove between the internal condyle and olecranon was found to be very shallow, owing, in two cases which were end results of old fractures, to an overgrowth of bone from the olecranon. In one instance a very definite bony spur of the ulna was present, without a history of fracture. It appears that the diffuse thickening of the nerve is due to frequent or constant but very slight trauma, such as bruising, or to the stretching of the nerve over some of the bony prominences. Small hemorrhages in the perineurium and in the endoneurium result, causing inflammatory reactions and the deposit of scar tissue. As the scar tissue tends to con-



[ Fig. 363.—Photograph illustrating the atrophy and the contraction due to a paralysis of the right ulnar nerve.

tract, many of the fibers become strangulated and eventually are destroyed, resulting in a gradual and progressive atrophy of the ulnar nerve.

#### REPORT OF THREE CASES

CASE 1 (82214).—R. L. K., a male, thirty-one years of age, fractured his elbow in 1892. The internal condyle was displaced downward and inward, thus giving the elbow a broadened appearance. The displacement of the internal condyle carried the ulnar nerve with it, leaving it in a very much exposed position on the apex of the displaced fragments, thus causing its frequent injury. Two months previously the patient received a very hard blow on the elbow. Following this he noticed marked numbness, slight loss of tactile sensation, and beginning atrophy of the small muscles of the hand, associated with corresponding weak-

ness. The weakness of the hand was progressive and surgical relief was advised and decided on (Fig. 364).

*Operation Jan. 17, 1918.*—The ulnar nerve was exposed in its extremely shallow groove, and the nerve was brought up over a portion of the internal condyle. For a distance of about 3 cm. the nerve was con-

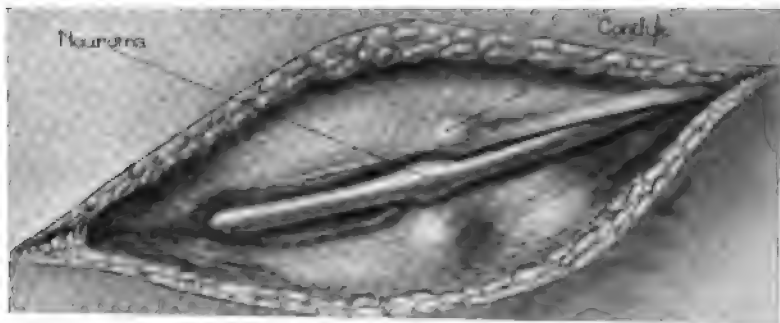


Fig. 364 (82214).—Exposure of the ulnar nerve with a neuroma due to trauma, without division of the nerve, associated with an old fracture of the elbow.

siderably thickened and presented a neuroma of about one-eighth the size of the normal nerve, situated over the most prominent portion of the internal condyle. The nerve was freed from the surrounding structures and transferred to a position internal to the condyle.

**CASE 2 (220582).**—J. A. L., a farmer, aged forty-two years. Four years previously the patient had first noticed numbness and tingling

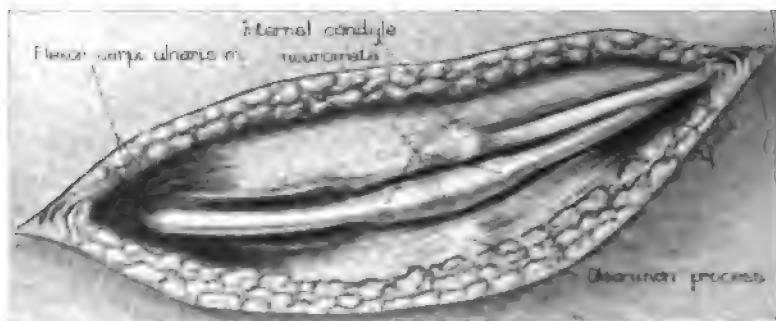


Fig. 365 (220582).—Exposure of the right ulnar nerve in position, illustrating three small neuromas in the nerve, due to trauma without severance of the nerve or fracture of the elbow.

sensations in the right little finger and on the ulnar side of the ring finger. Afterward he noticed that those two fingers became cold sooner than other parts of the hand; a little later he noticed that the hypothenar surface of the hand became very thin and flabby; then a marked depression appeared between the base of the thumb and the second metacarpal

bone, together with atrophy of the muscles of the outer part of the right forearm. About six months previously the patient had noticed that when he flexed the forearm on the brachial region the numbness and tingling sensations were increased, with associated pain above the right clavicle. At the time of examination he complained of more or less constant numbness and of a tingling sensation along the course of the ulnar nerve. There was marked atrophy of the small muscles of the hand; the flexor carpi ulnaris and part of the flexor profundus digitorum presented a decidedly thickened and nodular nerve in the ulnar groove (Fig. 365).

*Operation Feb. 9, 1918.*—There was a fusiform thickening of the ulnar nerve for about 4 cm. over the prominent portion of the elbow. In addition there were many adhesions about the nerve, and three neuromas, which were about one-fourth the size of the normal nerve, the latter situated so that each came in contact with the other in the

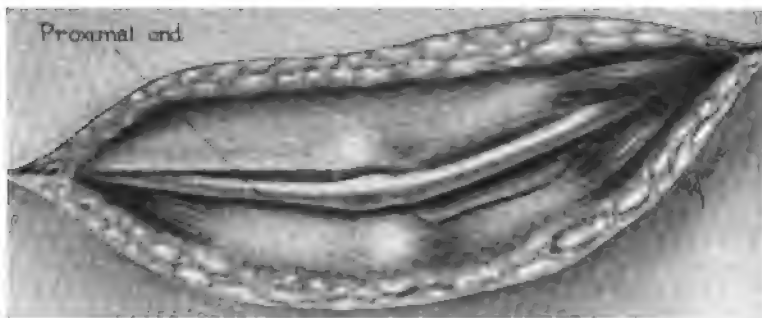


Fig. 366.—Exposure of left ulnar nerve with two neuromas due to trauma, associated with an old fracture of the elbow.

thickened portion of the nerve. The ulnar groove between the condyle and the olecranon process was normal in its depth when the arm was extended, but on flexion of the forearm a bony prominence, a spur from the ulna, presented itself, which exposed the ulnar nerve and produced a constant irritation.

**CASE 3 (222410).**—Mrs. J. S. D., aged thirty-two years, complained of numbness and a tingling sensation on the outer surface of the hand and forearm. There were atrophy and weakness of the muscles. Twenty-three years previously the patient had had a fall which resulted in the epiphyseal separation of the humerus at its lower extremity. Two years after the first fracture she had had a similar experience, but at that time there was no ulnar disturbance. Five years previous to our examination the patient first noticed numbness, more or less constant, in the little finger of the left hand, and three years later she noticed a beginning contraction of the two outer fingers of the left hand, which was associated with a thinning of the hand and a gradual loss of strength.



## RESULTS OF OPERATION

Three patients recovered after the removal of the tumors, 2 have improved to such a degree that they are able to take up their regular work, although there still is some weakness in one of the extremities. Two are slightly improved; they are able to control bladder and bowels, but are unable to work or go about. One patient improved markedly for ten months and returned to his regular duties, but he had a return of symptoms, and on a recent examination and re-operation we found a lordosis with compression of the spinal cord. There was no recurrence of a tumor, but many adhesions had formed, and destruction of the cord itself had taken place at the lower part of the curve. This apparently was due to the lack of support, as the cervical vertebræ had separated and slipped forward. The prognosis at this time, naturally, is very poor, even though the patient's convalescence has been uneventful. Improvement always takes place rapidly, and recovery is more complete and rapid in cases in which the symptoms have been of short duration and the paralysis has existed for less than a year. In the 5 cases in which we were unable to remove the tumors we performed an extensive decompression and left the dura unclosed. Two of these were cases of intramedullary tumors, 1 was a case of degenerative fibroma, and the other was so necrotic that a diagnosis was not made. One patient presented a definite history of lues that had been treated without results; he also had a definite sensory level. In view of this an exploratory operation was done and an angioma of the cord was found which we did not attempt to remove but merely ligated the vessels en masse. The patient has made a steady and progressive recovery, and at the present time is able to go about his regular work. A fourth patient in this group gave a definite history of a unilateral lesion, and on operative exposure a unilateral, infiltrating, inflammatory tumor was found. We were unable to remove the tumor on account of its extensive involvement in the cord itself and, unfortunately, the patient has not improved. The post-operative convalescence was complicated by the opening of the wound and the drainage of cerebrospinal fluid on the ninth day. The drainage continued for a week, but subsided without any particular treatment except that of placing the patient in the prone position over several pillows and lowering the head, strapping the wound together with adhesive strips, and the application of sterile dressings. In the fifth case of non-removable tumors there was a definite

history of lues nine years previously, with a development of a spastic paraplegia and a definite sensory level. Because of our findings and the negative specific tests, we advised an exploration. A gumma of the cord involving the meninges was found. Again, results were unsatisfactory.

In addition to the operations in the 13 cases of spinal cord tumors, we explored in 3 cases in which the lesions were questionable, and found meningomyelitis, with increased cerebrospinal pressure. The results in the 3 cases were as follows: One patient did not improve and gradually became worse; the second patient recovered, and at present is doing his regular work, and the third died on the second day, with a typical picture of fat embolism. This was the only death in the series.

### SUMMARY OF RESULTS

In the 16 laminectomies the removal of the tumor was effected in 8. Three of these patients have recovered; 2 have improved greatly, 2 have improved slightly, and 1 has a return of the trouble. There were no deaths. In the 5 instances in which the tumors were not removed 1 patient was greatly improved; 2 were improved slightly, and 2 were unimproved. One of the 3 patients with meningomyelitis recovered, 1 did not improve, and 1 died.

TABLE 1

Tumors located at time of operation . . . . .	83.60	per cent
Tumors removed . . . . .	61.70	"
Patients recovered . . . . .	25.00	"
Patients greatly improved . . . . .	18.75	"
Patients slightly improved . . . . .	25.00	"
Patients unimproved . . . . .	18.75	"
Mortality . . . . .	6.25	"
<hr/>		
Total patients improved . . . . .	68.75	"
Total patients unimproved . . . . .	31.25	"

### CONCLUSIONS

1. Neurologic examination is essential in all spastic paraplegias.
2. If the patient presents sufficient signs of a cord tumor, he should be given the advantage of an exploration.
3. A certain percentage of patients who have had spinal cord tumors removed recover completely.
4. A large percentage improve greatly.

TABLE 2.—RESULTS OF THE SURGICAL TREATMENT OF SPINAL CORD TUMORS\*

Case	Age	Sex	Neurologic Diagnosis	Surgical Findings	Location	Level	Duration of Illness	Recovered	Improved	Unimproved	Death	Remarks
Mr. W. A. M.	30	M	Spinal cord tumor	Psaemnoma	Subdural but extradural	Thoracic	10 mos.	Yes	..	..	0	Rapid improvement.
Mrs. C. A.	57	F	Spinal cord tumor	Psaemnoma	Subdural but extradural	Thoracic	2 yrs.	Yes	..	..	0	Rapid improvement.
Mrs. W. M.	40	F	Spinal cord tumor	Glioma	Subdural but extradural	Thoracic	3 yrs.	..	Slight bladder control	..	0	Slow improvement. Had cystitis.
Mrs. J. B. P.	45	F	Spinal cord tumor	Psaemnoma	Subdural but extradural	Cervico-thoracic	3½ yrs.	Yes	..	..	0	Moderately rapid improvement.
Mr. C. L.	35	M	Spinal cord tumor 50 per cent Myelitis 50 per cent	Psaemnoma	Subdural but extradural	Thoracic	7 yrs.	..	Slight bladder control	..	0	Slow improvement.
Mr. W. D.	45	M	Spinal cord tumor	Fibroma	Subdural but extradural	Cervical	3 yrs.	..	Marked 10 mos. for Relapse	..	0	Reoperated. Pressure on cord due to developing lordosis.
Mrs. S. E. D.	55	F	Spinal cord tumor	Psaemnoma	Subdural but extradural	Dorsal	2 yrs.	..	Marked	..	0	Rapid improvement.
Mrs. T. E. Y.	42	F	Spinal cord tumor 75 per cent Myelitis 25 per cent	Angioneuroma	Extradural	Dorsal	6 mos.	..	Marked	..	0	Slow improvement.

\* 8 tumors removed in 1917:

5 Psaemnoma

1 Glioma

1 Angioneuroma

1 Fibroma

7 Tumors were subdural but extradural

1 Tumor was extradural

Three patients recovered; 2 were markedly improved; 2 slightly improved; 1 improved markedly for ten months and then relapsed and was re-operated on. A compression of the cord was found due to a developing lordosis.

TABLE 3.—RESULTS OF THE SURGICAL TREATMENT OF SPINAL CORD TUMORS\*

CASE	AGE	SEX	NEUROLOGIC DIAGNOSIS	SURGICAL FINDINGS	LOCATION	LEVEL	DURATION OF ILLNESS	RECOVERED	IMPROVED	UNIMPROVED	DEATH	REMARKS
Mr. J. J. O. 170611	29	M	Spinal cord tumor? History of lues	Angioma	Intramedullary	Dorso- lumbar	10 mos.	..	Marked 85 per cent	..	..	Improvement slow.
Miss G. H. 209523	21	F	Spinal cord tumor 50 per cent Gumma?	Intra- medullary fibroma	Intramedullary	Cervico- thoracic	Onset 7 yrs. 1 yr. marked	..	Slight blad- der control	..	..	Improvement slow.
Mr. A. W. E. 130521	41	M	Myelitis 50 per cent Spinal cord tumor	Intramedul- lary tumor?	Intramedullary	Cervico- thoracic	Onset 8 yrs. 18 mos. marked	..	Slight blad- der control	..	..	Improvement slow.
Mrs. M. 206210	32	F	Spinal cord tumor	Unilateral Inflammatory mass	Intramedullary	Dorso- lumbar	18 mos.	..	..	Yes	..	Drainage of spinal fluid.
Mr. C. C. 210045	40	M	History of lues with level signs	Gumma	Intramedullary	Dorsal	18 mos.	..	..	Yes	..	..
Mr. J. R. W. 182125	46	M	Spinal cord tumor?	Meningo- myelitis	Intramedullary	Dorsal	12 mos.	..	..	Yes	..	..
Mr. B. 181084	31	M	Spinal cord tumor? Syringomyelia?	Meningo- myelitis	Intramedullary	Cervico- thoracic	12 mos.	Yes	..	..	..	..
Mr. M. O. B. 186135	31	M	Chronic mening.? Cord tumor. His- tory of mening. nine years ago	Meningo- myelitis	Intramedullary	Cervical	Onset 9 yrs. 1 yr. marked	..	..	..	Yes	Death thirty hours after operation. Fat embol- ism.

\*Two intramedullary tumors; 1 angioma or varicose veins of the cord; 1 unilateral inflammatory tumor; 1 gumma of cord and meninges; 3 meningomyelitis. One angioma markedly improved; 2 intramedullary tumors slightly improved; 1 with inflammatory mass unimproved; 1 gumma unimproved; 1 meningomyelitis recovered; 1 meningomyelitis unimproved; 1 meningomyelitis died.

5. Although improvement is slight in some instances an exploratory laminectomy is justifiable on the grounds that one is unable to say, prior to operation, whether or not the tumor is removable.

TABLE 4.—SUMMARY OF RESULTS OF THE SURGICAL TREATMENT OF SPINAL CORD TUMORS\*

LAMINECTOMY WITH EXPLORATION OF CORD		RE- COVERED	GREATLY IMPROVED	SLIGHTLY IMPROVED	UNIM- PROVED	RETURN OF TROUBLE	DEATH
Tumors removed.....	8	3	2	2	..	1	..
Tumors not removed, but pa- tient decompressed.....	5	..	1	2	2	..	..
Meningomyelitis.....	3	..	..	..	1	..	1
Total.....	16	4	3	4	3	1	1

\* Percentage of tumors located, 83.6; of tumors removed, 61.7; of patients recovered, 25; of patients greatly improved, 18.75; of patients slightly improved, 25; of patients unimproved, 18.75; of mortality, 6.25 per cent. Total percentage of patients improved, 68.75; of patients unimproved, 31.25.

## TECHNIC



## THE USE OF SODIUM BROMID IN RADIOGRAPHY\*

E. H. WELD

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In the past, various substances have been used as opaque mediums in pyelography. Among such substances may be mentioned bismuth, the colloidal silver solutions (collargol, argyrol, electrargol, cargentos, etc.), and several preparations of silver iodid and thorium. Many of these substances, when retained in the renal pelvis, have a more or less irritating action on the kidneys, as has been demonstrated experimentally by Braasch and Mann, who injected the kidney pelves of 67 dogs and compared the effects of a variety of solutions. The results of their experiments show that the silver preparations act as foreign bodies, frequently causing multiple foci of necrosis, and that such focal necrosis may also occasionally occur when there is insufficient drainage from a kidney pelvis, even when bland fluids are used. Thorium nitrate in a 15 per cent solution, as suggested by Burns, caused the least reaction of the various opaque mediums. This medium has been widely used in pyelography, and, until recently, was considered the best one available, the greatest objections to it being the chemical difficulties in its preparation and the excessive cost. More recently Cameron has advocated the use of potassium iodid in a 25 per cent solution, which appears to be fully as opaque to the x-ray as thorium; it has the advantage of being easily prepared, and is somewhat less expensive.

The ideal medium for pyelography should be non-toxic, non-irritating, and easily soluble in urine—one that can be sterilized, that keeps well under all conditions, and may be procured at a reasonable cost. In experimenting with various solutions in order to determine their opacity when rayed, we found that the bromids were quite as satisfactory as any of the other solutions, and in many cases it was only necessary to use a 12.5 per cent solution to obtain a readable pyelogram or cystogram.

\* Reprinted from Jour. Am. Med. Assn., 1918, lxxi, 1111-1112.



It would seem that the opacity of various solutions should vary as directly as their atomic weights. However, there is little or no difference in the opacity of the solutions of the same strength, whether bromids or iodids (Fig. 372). Severe reactions have been observed in several patients, when potassium iodid in 25 per cent solutions was employed. This was evidently due to local irritation. The bromids have not appeared to be so irritating as the iodids. Bromid salts are freely soluble in urine, so that their irritating action is continually lessened by dilution with urine from the time that they are injected. They are excreted very largely by the kidneys, and no deleterious effect on the substance of the



Fig. 372.—Comparison of different solutions; radiograms taken in 8 c.c. bottles.

kidneys has been noted. The toxic effect that might be produced may be disregarded, because as much as 8 or 10 gm. of the salts have been given by mouth without producing any untoward symptoms, and it is unlikely that there is much absorption in the genito-urinary tract. Probably no sedative effect would be noted.

The opacity appears to be due almost entirely to the bromid radical, as it is shown that when sodium chlorid is used, little or no retardation of the x-ray is noted. Sodium bromid, apparently, smears over the surface of the ureters, minor calices of the kidneys, and small saccules of an inflammatory bladder even much better than thorium, and for this reason we believe has a distinct advantage over it. Furthermore, the

drug is easily obtained, and costs only 75 cents a pound at the present time, whereas potassium iodid costs \$4.90 a pound, and thorium, even in a 15 per cent solution, largely because of the difficulty in its manufacture, costs \$2.50 a pound.

We have injected 2 c.c. of 25 per cent sodium bromid in the ureters of three dogs, in which the ureters were ligated and divided immediately after injection. Six days later a nephrectomy was performed and a hydronephrotic sac containing approximately half an ounce of fluid was



Fig. 373.—Pyelogram with 25 per cent sodium bromid solution; slightly dilated pelvis; normal calices; lead catheter on left.

found. Macroscopic and microscopic examinations of these kidneys did not show any irritating effects from the drug. We have used a 12 per cent solution of sodium bromid in making several cystograms on patients, and a 25 per cent solution of sodium bromid in making several pyelograms, without noting any injurious effects (Figs. 373, 374, and 375).

Experiments are now under way for the purpose of comparing the effect of thorium, potassium iodid, and sodium bromid, when they are retained in kidney pelves, and also for the purpose of studying the gradual development of hydronephrosis after the injection into the

kidney pelvis of various opaque solutions. The sodium bromid is easily procured, easily sterilized, and is inexpensive. In our experience sodium bromid in a 25 per cent solution has offered advantages as a medium for pyelography as follows:

1. It is a bland solution and does not damage the kidney.
2. It casts a clear shadow, outlining the entire pelvis and ureter, as well as, if not better than, other mediums thus far advocated.
3. It is less irritating to the pelvic and vesical mucosa than other mediums.
4. It is the least expensive, and is readily procured.
5. It is very easily prepared, and is readily sterilized by boiling.

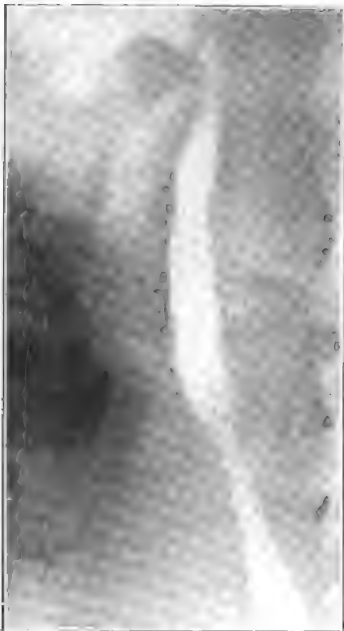


Fig. 374.—Pyelogram with 25 per cent sodium bromid solution; marked inflammatory dilatation of calices and ureter



Fig. 375.—Cysto-ureteropyelogram with 25 per cent sodium bromid solution; bilateral ascending pyelonephro-ureteritis, cystitis, and distorted bladder.

# A "SCHREIBER" ADAPTER FOR INTRAVENOUS INJECTIONS\*

J. H. STOKES

Those who appreciate the good qualities of the Schreiber needle in meeting the difficulties of intravenous injection technic will appreciate



Fig. 376.—*A*, Conventional type of Schreiber needle; *B*, Schreiber adapter with two different types of needles; *C*, Schreiber adapter with 22-gage hypodermic needle attached.

the serviceability of the device here illustrated, which has been in use in my service for several months. The Schreiber needle is made in only one, or at most two sizes. This adapter makes possible the use of a needle of any size desired to meet the indications in a particular case. The needle

\* Reprinted from the Jour. Am. Med. Assn., 1918, lxxi, 108.

proper is attached to the standard Luer hub of the adapter, and adapter and needle are then used together as one instrument in accordance with a technic that I have already described.\* The device was developed in coöperation with Mr. P. L. Pinkerton, of the Precious Metals Tempering Company, who submitted a sketch and later a specimen for clinical trial. Whenever, for any reason, it is found necessary to inject amounts of solution too large to be readily administered with a syringe into small or difficult veins, such as those of the scalp, hand, and wrist, this adapter has proved exceedingly useful.

\* Stokes, J. H.: Certain technical refinements in methods of intravenous injection, *Med. Rec.*, 1917, xcii, 529-535.

## HYPOPHYSEAL TUMORS THROUGH THE INTRA-DURAL APPROACH\*

A. W. ADSON

My attention was first called to the intradural approach for the removal of hypophyseal tumors by Dr. G. H. Heuer, of Johns Hopkins Hospital. Dr. Heuer showed me two patients on whom he had operated by this method. I shall not discuss the surgical indications of hypophyseal disorders, but in the group of cases in which there were visual disturbances, the improvement following operation has been so marked that we feel that special attention should be called to the surgical treatment. Six patients have been operated on, and drawings are presented which show the tumors in place before their removal. The physiologic and surgical indications of hypophyseal tumors have been described by Cushing. Frazier has called attention to three surgical indications: (1) Subtemporal decompression for the relief of pain; (2) decompression of the sella turcica or removal of the tumor for visual disturbances, and (3) operation on the pituitary body for amelioration of hyperpituitarism.

The first successful hypophyseal operation was performed by Schloffer in 1907 through the extracranial transsphenoid approach. Several modifications of this technic have been made by Hirsch, von Eiselsberg, Cushing, Kanavel, and others. In 1893, the subtemporal operation by the intracranial method was done by Thus, Caton and Paul. Krause, in 1905, and Hartley and Kiliani in 1904, attempted to expose the hypophysis by bilateral osteoplastic frontal resection and ligation of the longitudinal sinus. Kiliani suggested opening the dura as soon as the osteoplastic flap was removed. Frazier, in 1913, described the transfrontal approach, which differed from the technic of McArthur in that the osteoplastic flap was turned in conjunction with the resection of the roof of the orbit. In both the McArthur and the Frazier operations the dura was raised with the frontal lobe and not opened until the anterior clinoid process was approached.

\* Reprinted from Jour. Am. Med. Assn., 1918, lxxi, 721-726.

## TECHNIC

The technic herein described is of an intradural approach after an osteoplastic flap has been turned from the right frontoparietal region. The dura is opened widely to permit the exposure of the frontal lobe, which is protected with cotton and rubber tissue. The lobe is then elevated gently until the optic commissure and the hypophysis are exposed.

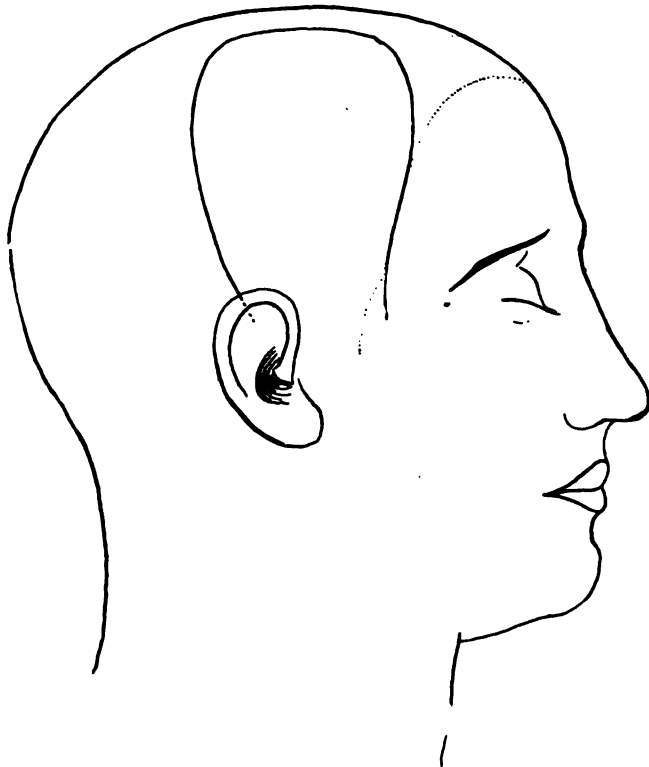


Fig. 377.—Osteoplastic flap previous to exposure of frontal lobe and pituitary gland.

The patient is anesthetized by the inhalation drop method and placed on the operating table at an angle of 80 degrees with the horizontal plane. The head is held back in a position to permit the natural gravitation of the frontal lobe from the anterior cranial fossa. The anterior limb of the osteoplastic flap corresponds to the margin of the hair-line, and this affords three-fourths inch of space posterior to the external angular process of the orbit, thus preventing injury to the motor branch

supplying the frontal division of the occipitofrontalis and guarding against any paralysis of the muscle. The incision is carried upward to the median line, three-fourths inch from the longitudinal sinus; it is then extended backward for a distance of  $3\frac{1}{2}$  inches and downward over



Fig. 378 (Case 4).—Operative scar, eight days after operation, showing its relation to the hair-line. No paralysis of the occipitofrontalis muscle.

the parietal eminence to a position above the middle portion of the ear (Figs. 377 and 378).

The bleeding in the flap is controlled by the application of a pedicle clamp\* at the base of the flap (Fig. 379). The bleeding in the scalp, aside from that in the flap, is controlled by the application of forceps to the aponeurosis (galea), one-half inch apart and turned outward to compress

\* I am indebted to Dr. Heuer for the method of applying the pedicle clamp.



gently the margin of the skin. The forceps are tied in groups and left in position during the operation (Fig. 379). The bone flap is turned by the use of the Hudson drill (the de Vilbiss) on the sides and the Gigli saw on the upper margin. This produces the beveled effect which assists in holding the flap in place as a lid.

After the dura has been exposed, a flap is made to permit the exposure of the frontal lobe, but it is made at right angles to the osteoplastic

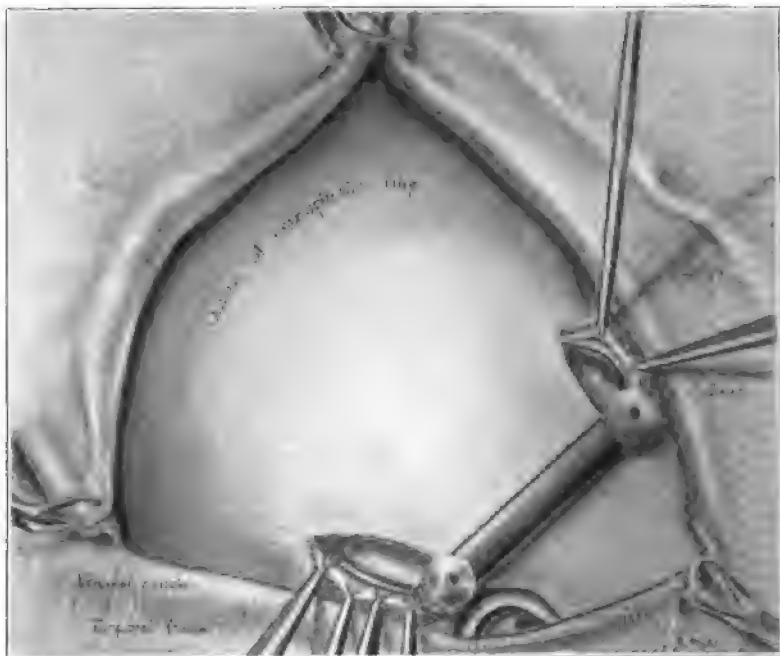


Fig. 379.—Pedicle clamp to control bleeding in the osteoplastic flap. Forceps on the aponeurosis to control bleeding along outer margin of incision.

flap, which has been broken in the region of the temporal bone and turned downward. The dural flap is permitted to remain in position and to cover the cortex of the brain, and the frontal margin is raised by tension sutures of silk. The brain substance, as well as the exposed dural surface, is covered with warm, moist cotton, which, in turn, is covered by rubber tissue (Fig. 381).

In the elevation of the frontal lobe rubber tissue strips are placed gently over the convolutions in a shingle effect, in order to give a uniform

pressure over the cortex as it is elevated by the retractor\* (Figs. 381 and 382). There is very little difficulty with bleeding during this process; occasionally there is a small venous communication between the cortex and the dura. With gentle manipulation the optic commissure and the hypophyseal body are readily exposed. Important landmarks during the elevation of the frontal lobe are the anterior cranial fossa, the margin of the lesser wing of the sphenoid to the anterior clinoid process, the

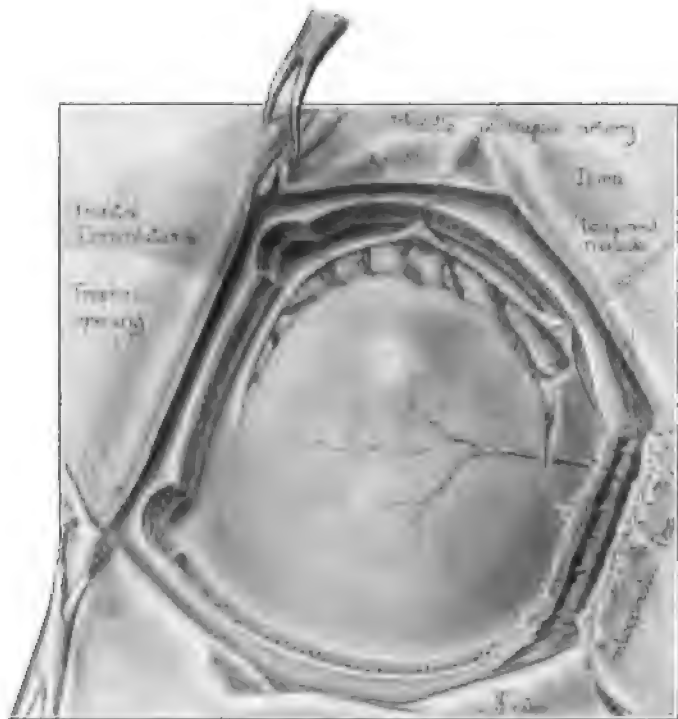


Fig. 380.—Exposure of the dura, which is divided along its anterior margin to permit the exposure of the frontal lobe.

right optic nerve, and the internal carotid artery. The procedure is then carried on mesially until the commissure as well as the left optic nerve and the hypophyseal body are brought into view (Fig. 383). A gentle dissection of the tumor is then begun with blunt hooks to free it from the commissure, nerves, and surrounding tissue. Usually the tumor is

\* This retractor is arranged with a small laryngoscopic light which illuminates the region of the optic commissure much better than a reflector or head light. The retractor is similar to the one used by Frazier. We have also made a curet forceps to scoop out the cellular tissue from the sella.

definitely encapsulated, and if freed from the constricting bands, it is readily elevated. In case there is slight bleeding, it is controlled by very small pledgets of cotton guarded by long strings of silk to prevent their loss. As the tumor is freed from the surrounding structures (Fig. 384) a septile snare is applied to its pedicle, which is gradually constricted to control the bleeding and to remove the tumor mass (Fig. 385). The

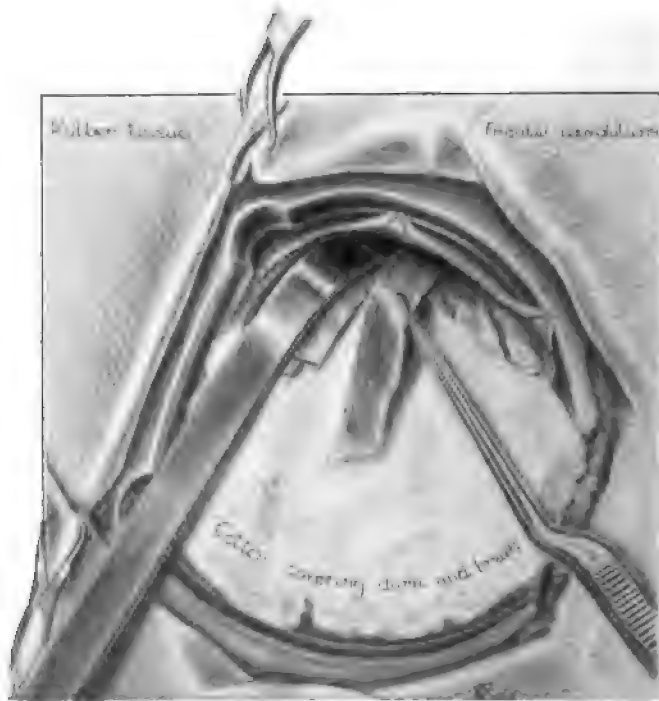


Fig. 381.—Elevation of the frontal lobe with the insertion of rubber tissue strips, which are applied as a protection to the brain cortex.

further removal of the pituitary body from the sella turcica may then be continued.

#### REPORT OF CASES

**CASE 1 (201188).**—Mrs. J. J. L., a housewife, aged fifty, examined, July 18, 1917, for the past fifteen months had noticed a gradual failing in vision, particularly a narrowing of the temporal fields. She was unable to see approaching objects from the side. She also complained of marked dyspnea. The general examination was negative except for hypertension. The systolic blood-pressure was 210, the diastolic 114.

The urine, blood, and Wassermann tests were negative. The combined functional phenolsulphonephthalein test was 60 per cent in two hours. The x-ray examination of the head revealed the sella to be moderately enlarged. The nerve-heads of the eyes were slightly pale, the physiologic cup deep and broad, and the arteries small. The tension by the Schiötz tonometer was 18 in both eyes. The left temporal field presented an absolute hemianopsia with constriction on the nasal side. In the right temporal field there was hemianopsia except for a slight vision on the lower temporal margin. The nasal field was quite normal. Operation was performed, Aug. 22, 1917. On exposure of the hypophyseal region,

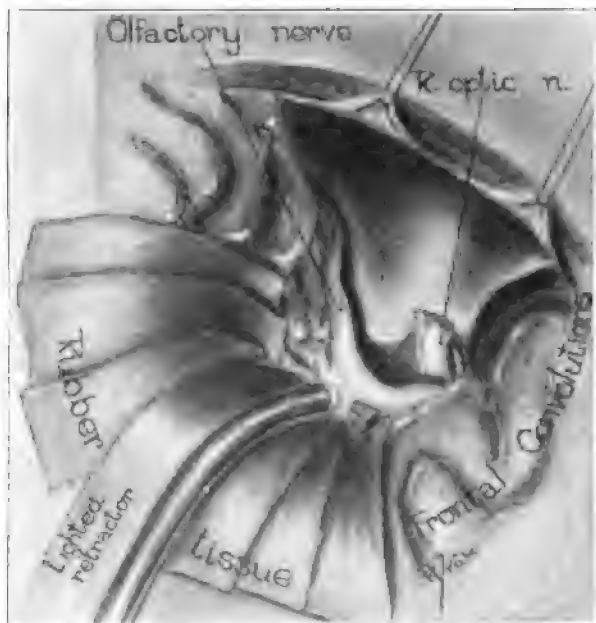


Fig. 382.—Elevation of frontal lobe, exposing right olfactory nerve and right optic nerve prior to exposure of pituitary tumor.

a pituitary tumor about an inch in diameter, soft but well encapsulated and bluish gray in appearance, was found. The tumor was situated in the sella and seemed to rise under the left optic nerve. On removal of the mass some erosion was noted in the right margin of the sella. About one-fourth of the normal gland was left in the sella. The patient's post-operative convalescence was uneventful. Eight fields were made from the time of operation until September 29, when there was a complete return of normal object as well as color-fields. In a letter from the patient three months after the operation, it was stated that vision was still perfectly normal (Figs. 383 and 384).

**CASE 2 (207683).**—Mrs. A. E. S., a housewife, aged twenty-eight, examined Oct. 11, 1917, complained chiefly of blindness, most noticeable in the left eye, and with a gradual diminution of vision on the sides. This began twelve months previous to examination. Three and one-half months previously there had been rapid loss of vision in the left eye. Four months previous to her examination the menstrual flow ceased and did not return. There was no pregnancy. She complained more or

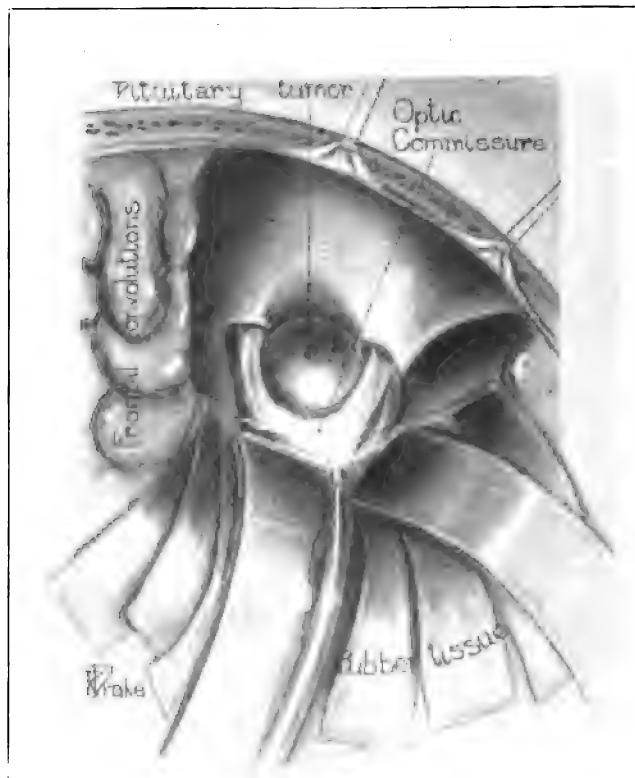


Fig. 383 (Case 1).—Exposure of pituitary tumor, with relation to optic nerves and commissure with a bitemporal hemianopsia, which is more marked in the left eye.

less of marked drowsiness, and slept much of the time. She had gained in weight in the last four months, and her hands and feet had become slightly enlarged so that she was obliged to increase the size of gloves and shoes. The systolic blood-pressure was 100, the diastolic 64. The urine, blood, and Wassermann tests and the radiogram of the sella were negative. The vision in the right eye was  $\frac{2}{200}$ ; there was no vision in the left eye. The right nerve-head was pale on the nasal side; the margin was well defined. The fields were absent on the left, and there

was absolute temporal hemianopsia on the right. Operation was performed Oct. 1, 1917. On exposure of the hypophyseal body a dark red nodule, about three-fourths inch in diameter and completely encapsulated, was found situated anterior to the optic commissure, but beneath it and elevating the left optic nerve as well as the commissure. The right optic nerve was one and one-half times the normal size, and edematous. The tumor was very adherent to the sella on the anterior side. A small amount of the gland, about one-fourth the normal, was left in the sella. Immediately following the operation the patient developed a very high temperature (106) which continued until death, at the end of thirty hours. At necropsy, when the osteoplastic flap was reflected, a considerable amount of soft, dark, clotted blood adherent to its under surface was found. The leptomeninges were clear. There was no accumulation of blood inside the dura except a slightly blood-tinged serum down in the region of the sella. There was a marked general edema of the brain with a free flow of cerebral fluid from the right ventricle, which had been tapped during the operation to relieve the pressure and to permit a better exposure (Fig. 386, c).



Fig. 384.—Placing the snare about the pedicle of the pituitary tumor.

CASE 3 (207279).—J. L. W., a cashier, aged forty-two, examined Sept. 7, 1917, first noticed ten years previously that he had lost vision in the right eye. One year previously vision began to fail in the left eye, incapacitating him for work for the last eight months. The systolic blood-pressure was 159, the diastolic 101. The blood, urine, and Wassermann tests and the x-ray examination of the sella were negative. The right nerve-head was perfectly white, and there was an absence of visual field but no other fundus change. The nerve-head of the left eye was markedly pale along the nasal side. The vision was 3/200. There was blindness of the right eye and a constricted left temporal field—about one-third of the normal. No field whatever could be obtained with a candle on the right side.



Fig. 385.—Appearance of sella after tumor has been removed.

On operation, Oct. 10, 1917, a large, grayish-red tumor about an inch in diameter was exposed under the right optic nerve and optic commissure,

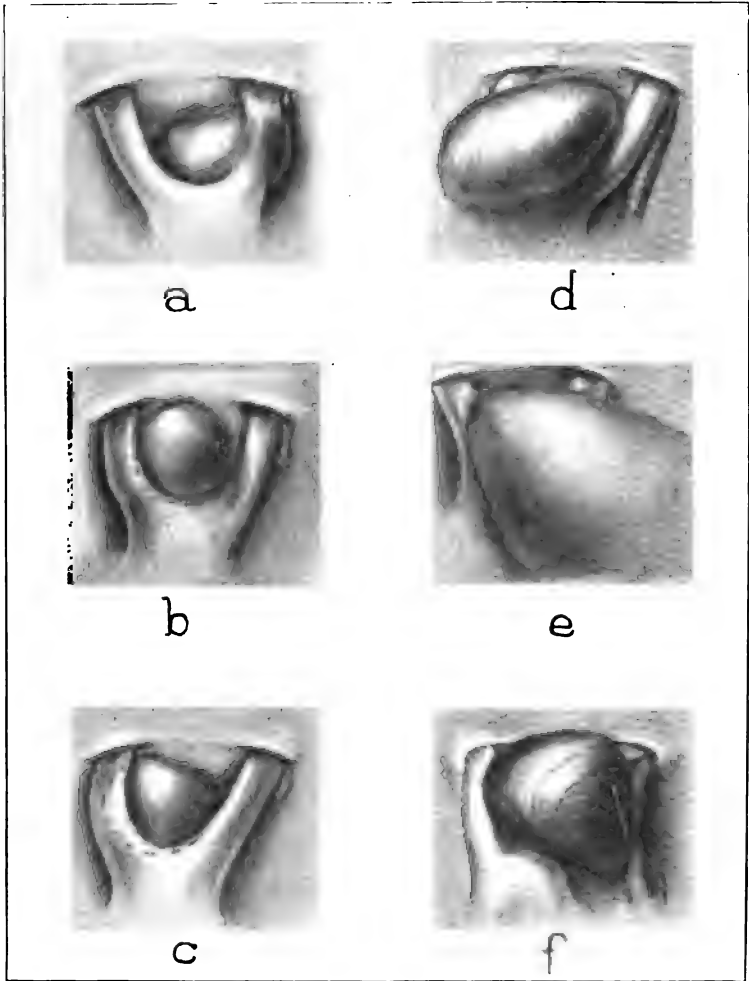


Fig. 386.—Exposure of pituitary tumor, with its relation to the optic nerves and commissure, producing: *a* (Case 3), total blindness of the right eye with a left temporal hemianopsia; *b* (Case 4), contracted left temporal field associated with typical symptoms of acromegalia; *c* (Case 2), total blindness of left eye and hemianopsia of right eye; *d* (Case 6), total blindness in left eye with temporal hemianopsia of right eye; *e* (Case 5), total blindness in right eye with a temporal hemianopsia in left eye, and *f* (Case 7), exposure of an intracranial projection of nasopharyngeal sarcoma producing total blindness in right eye and temporal hemianopsia in left eye.

making it necessary to dissect the fibers of the nerve out of the pituitary mass. A very small portion of the pituitary body—about one-fourth of a normal gland—was left in the sella. There was very rapid progress and

a return of the left temporal field with light and perception of moving objects in the right eye at the end of three weeks. When the patient reported for examination three months later there was marked improvement in the left eye, and he was able to see objects and to read large letters with the right eye, showing a decided improvement in the upper four-fifths of the nasal field as well as the outer, upper quadrant of the temporal field. The blue and red color-fields had also partially returned (Fig. 386, *a*).

CASE 4 (210605).—Mrs. T. E. B., a housewife, aged thirty-eight, examined Oct. 12, 1917, complained chiefly of eye trouble and abnormal enlargement of the feet, hands, and face. The patient had had amenorrhea since the birth of her last child, eight years previously. The visual disturbances dated back five years, the time of onset of the present acromegalic syndrome. The trouble had been progressive, with visual disturbance in the left eye, for the year preceding examination. She had been unable to see sufficiently to sew or to do fine work for several weeks. The general examination presented a typical picture of acromegalia. The systolic blood-pressure was 110, the diastolic 80. The urine, blood, and Wassermann tests were negative. The x-ray examination of the head revealed a markedly enlarged sella. The field in the right eye was quite normal as to object and color; the left temporal field, as well as the margin of the left nasal field, was markedly constricted as to moving objects, and there was a complete absence of color-fields. The fundus of each eye was negative. At operation, Oct. 25, 1917, a very soft, grayish pituitary tumor about one-half inch in diameter was found underneath the commissure and pushing upward slightly toward the left optic nerve. The tumor was completely removed and the sella curetted, leaving no possible trace of pituitary substance. The patient was immediately put on a pituitary extract, continued in alternating periods of ten days. Her recovery was rapid. There was a return of the color-fields in the left eye, and considerable change in the tissue of the face, hands, and feet at the end of three weeks. The mentality, which was very slow previous to operation, had greatly improved. The patient reported by letter about two months after operation, and stated that vision remained clear, that she was feeling better than she had felt for years, and that the swelling of the hands and feet was gradually diminishing (Fig. 386, *b*).

CASE 5 (45560).—Miss M. L., aged thirty-six, examined Oct. 23, 1917, two and one-half years before had had severe pain in the right side of the head, associated with a failing vision in the right eye which progressed until it was complete one year previously. Within the last year vision in the left eye had almost completely failed. At about the time the visual disturbances appeared the menstrual flow stopped abruptly. There had been occasional vomiting, with perversion of taste and smell. The systolic blood-pressure was 104, the diastolic 78. Urine, blood,



and Wassermann tests were negative. X-ray examination revealed the sella apparently greatly enlarged, and erosion of the posterior clinoid process. There was pallor of the right optic disk with complete blindness, an absolute temporal hemianopsia of the left eye, pallor of the nasal side of the optic disk, and a low grade of optic neuritis of the whole left nerve-head. There was no swelling of either nerve-head. A diagnosis was made of a basal tumor either coming from, or encroaching on, the pituitary gland. An exploratory operation through this pituitary route was advised and performed Nov. 1, 1917. The hypophyseal mass, which was situated under the right frontal lobe and very adherent to it, was exposed, but it was impossible to get below the tumor. The optic nerves could be seen, but only a partial removal of the tumor was accomplished because of the hemorrhagic condition. The post-operative convalescence was uneventful, but no benefit was derived from the operation except the relief from pain, which was obtained from the large decompression made at the base of the osteoplastic flap (Fig. 386, *e*).

CASE 6 (219123).—D. A., a girl, aged nine years, examined Jan. 1, 1918, for the past four years had had diabetes insipidus without glycosuria. Visual disturbance began three months previously with marked and progressive disturbance in the left eye. At the time of examination there was almost complete loss of vision in the left eye, and shortly afterward a marked loss of vision on the temporal side in the right eye. There had been nausea, vomiting, and mild headache over the left eye. The child appeared exceptionally bright and was well nourished. A twenty-four-hour specimen of urine, 1800 c.c., showed alkaline reaction, specific gravity 1.005, and a slight trace of albumin. The blood and Wassermann tests were negative. Radioscopy revealed enlargement of the sella, and a thinness of the posterior clinoid process and base. The left temporal field showed very slight light perception. The nasal field presented a marked constriction with distortion. The left nerve-head was swollen to the extent of 2 diopters; the veins were tortuous. An absolute temporal hemianopsia was present in the right eye, and in the fundus were a small disk, hazy, tortuous veins, and hyperemia of the nerve-head. There were no hemorrhages in either eye. Operation was performed Jan. 24, 1918, and a pituitary tumor about an inch in diameter was found underneath and bulging up over the optic commissure. It had originated from the pituitary gland and was extremely adherent to all the surrounding structures, with, however, a definite line of demarcation. In two places the growth had broken through the capsule and had become adherent to the brain substance. The tumor was removed with considerable difficulty, since it was impossible to get all of it from underneath the commissure. Because of the increased pressure on the brain, it became necessary to drain the lateral ventricle. There was marked progress in the return of the visual fields; the patient could read with the left eye at the end of two

weeks. Improvement of the right temporal field was slower than in the usual case. Eight weeks after the operation the patient was doing well, but the visual improvement was still slow (Fig. 386, *d*).

A case of nasopharyngeal tumor with intracranial projection (Fig. 386, *f*) producing visual disturbance is presented as a means of comparison.

CASE 7 (216363).—F. A. A., a man, aged thirty-three, examined Dec. 1, 1917, three years previously had noticed partial blindness in the right eye, and two and one-half years later vision completely failed. There had been no other disturbance since that time until three weeks previous to examination, when the patient complained of vertigo and headache. The systolic blood-pressure was 112, the diastolic 100. The urine and Wassermann tests were negative. An x-ray examination of the sella revealed complete erosion with destruction of the sphenoid body and cells. There was complete blindness in the right eye, absolute temporal hemianopsia in the left, a marked right optic atrophy, and hyperemia of the left nerve-head, but no swelling and no other fundus changes.

#### SUMMARY

In two of the group of six cases the patients presented very definite bitemporal hemianopsia, with more or less complete loss of vision in the left eye. One patient had a complete loss of vision in the right eye for a period of ten years, and a left temporal hemianopsia; one presented a typical acromegalic syndrome with a temporal color hemianopsia and constricted object field; one had bitemporal hemianopsia with more or less distorted fields in the left eye, and one had blindness in the right eye with definite neighborhood symptoms producing a frontal lobe syndrome of pressure and localization, involving the uncinate gyrus. Post-operative convalescence was uneventful and rapid in all but one case, in which the patient died on the second day. In two cases there was complete restoration of vision, in two marked improvement in vision, and in one a relief from headache. In the case of blindness in the right eye which was complete for ten years, the patient has begun to have a return of vision. The patient with acromegaly is having metabolic changes. In five cases there has been definite improvement. In one, no visual improvement, but relief from pain was obtained.

The particular advantages of the operation are: (1) Its approach presents a dry field, free from infection, and in which it is comparatively easy to expose the optic commissure and the tumor. (2) The exposure

permits the dissection of the tumor from the optic nerves and the commissure, and the removal of all or any portion of the tumor and pituitary body that is desired. (3) Trauma of the commissure and nerves is prevented, as the sponging is done against the floor of the sella instead of working upward against the commissure and nerve peduncles. So far as the operative risk is concerned, it is no greater than in craniotomies on the frontal lobe, depending a great deal, no doubt, on the experience of the operator.

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## FURTHER EXPERIENCES WITH THE KONDO- LÉON OPERATION FOR ELEPHANTIASIS\*

W. E. SISTRUNK

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I wish to discuss in this paper the merits of the Kondoléon operation for elephantiasis and to report the results obtained in seven patients operated on by the method.

Kondoléon of Athens, Greece, in 1912, first reported cases of elephantiasis in which operation was performed by his method. The operation seems to have been gradually evolved through others of a similar though distinctly different type, which had been performed by Lanz, Oppel, and Rosanow, and its aim is to establish, by a wide excision of the aponeurosis, a communication between the superficial and deep lymphatic channels. The deep aponeurosis seems distinctly to separate the superficial from the deep group of lymphatics. In elephantiasis, the edematous and hypertrophied tissues are found to lie above the aponeurosis, while the subaponeurotic tissues are usually quite normal. When large pieces of this tissue are removed, sufficient communication may be established to allow the deeper group of lymphatics and the muscles to drain the stagnant lymph ordinarily handled by the blocked superficial group, and this very markedly benefits the condition. The technic of Kondoléon's operation is as follows:

Long incisions are made along the outer and inner aspects of the affected limb, and through each of these a large slice of edematous fat is removed. The aponeurosis is then opened, and a portion of it, three or four fingers in width, is excised throughout the entire length of the skin incision. The wound is then closed without drainage in such a way that the skin, with a small amount of subcutaneous fat attached to it, comes in contact with the exposed muscles.

The first article in this country calling attention to and commending this operation was published in 1913 by Matas of New Orleans. He dis-

\* Presented before the Section on Surgery, General and Abdominal, at the Sixty-ninth Annual Session of the American Medical Association, Chicago, June, 1918. Reprinted from Jour. Am. Med. Assn., 1918, lxxi, 800-805.

cusses in detail the etiologic factors that contribute to the production of true elephantiasis, giving his own opinion and that of others regarding the part which bacteria, usually streptococci, play in the production of this condition, and emphasizing repeatedly the necessity of such bacterial invasion in order that a true elephantiasis may be produced. Lymphatic or venous stasis, from various causes, usually precedes and is the predisposing cause of the bacterial invasion, although, according to Matas, many writers, including Le Dantec, Sabouraud and Unna, believe that true elephantiasis may occur independently of lymphatic or venous obstruction and solely as a result of repeated attacks of streptococci infection. Matas states that the histopathologic elements that are essential to complete the picture of elephantiasis are—(1) A mechanical obstruction or blockade of the veins and lymphatics of the affected region, usually an obliterative thrombophlebitis or lymphangitis or adenitis; (2) hyperplasia of the collagenous connective tissue of the hypoderm; (3) gradual disappearance of the elastic fibers of the skin; (4) the existence of a coagulable dropsy or hard lymphedema, and (5) a chronic reticular lymphangitis caused by secondary and repeated invasion of pathogenic microorganisms of the streptococcic type. In conclusion he reports two cases in which operation was performed, one by himself and the other by his associate, Gessner, which were the first cases in this country in which the Kondoléon operation was used.

Royster, early in 1914, reported a case in which operation was performed by Kondoléon's method, and Hill, in 1915, reported a case in which the same procedure had been used.

The operation has been performed in the Mayo Clinic in 7 instances. I have reported 3 of these cases in a recent article on the subject. In 3 of the patients the disease was located in the left arm, and in the other 4 patients in one of the lower extremities.

In the first arm case an elephantiasis had developed following an infected vaccination wound, with repeated erysipelatous attacks in the affected arm. The next arm case in which operation was performed was one of a simple lymphedema of the arm following the radical removal elsewhere of the left breast and axillary glands for a supposed malignant tumor of the breast, but which was afterward proved to be benign. In the third arm case, an elephantoid condition had resulted from an injury to the arm two years previously.

In one of the leg cases, a woman aged twenty-three, the condition was probably congenital, having been first noticed when the patient was

a child one and one-half years old. In another case of a girl, aged seventeen years, who had had trouble for six years, no etiologic factor was obtainable. Her tonsils were septic, and were removed following the operation. The third leg case in which operation was performed was that of a child with a chronic tuberculous synovitis of the knee and tuberculosis of the inguinal lymph-nodes on the affected side. The fourth case was in a woman of twenty-one. The condition had developed six years previously, following an attack of tonsillitis, with subsequent arthritis which was accompanied by fever. At the same time she also had four large boils on her face and right arm.

In all of the leg cases there was marked thickening of the dermal and hypodermal tissues, with marked edema and thickening of the aponeurosis, but in none of these could a history of recurring erysipelatous attacks be obtained.

The results obtained in the arm cases were not so satisfactory as those in the leg cases. In each case improvement was quite marked shortly after the operation, but in two instances the patients still report some swelling which fluctuates in its extent. In the patient in whom the trouble had developed following vaccination, the arm and forearm have returned to normal, but a swelling of a fluctuating type still persists on the dorsal surface of the hand.

In all of the leg cases the improvement was very striking and occurred almost immediately following operation. In the first of these operation was performed one and one-half years ago (previous to June, 1918), and the others eight months, four months, and two months ago respectively. All were heard from or seen during April or May, 1918, and in each case the improvement has been very marked and has persisted.

We were able to grow streptococci from the verrucose formations which were present in certain areas on the arm of the patient who developed elephantiasis following infection in the vaccination wound. However, although cultures were made from the edematous fat and thickened aponeurosis in nearly all of the other cases in which operation was performed, streptococci or other pathogenic organisms could not be grown. In the first patients operated on no microscopic examinations were made of the tissues removed. In the later cases, however, careful examinations of these were made with the same findings as those reported by other writers.

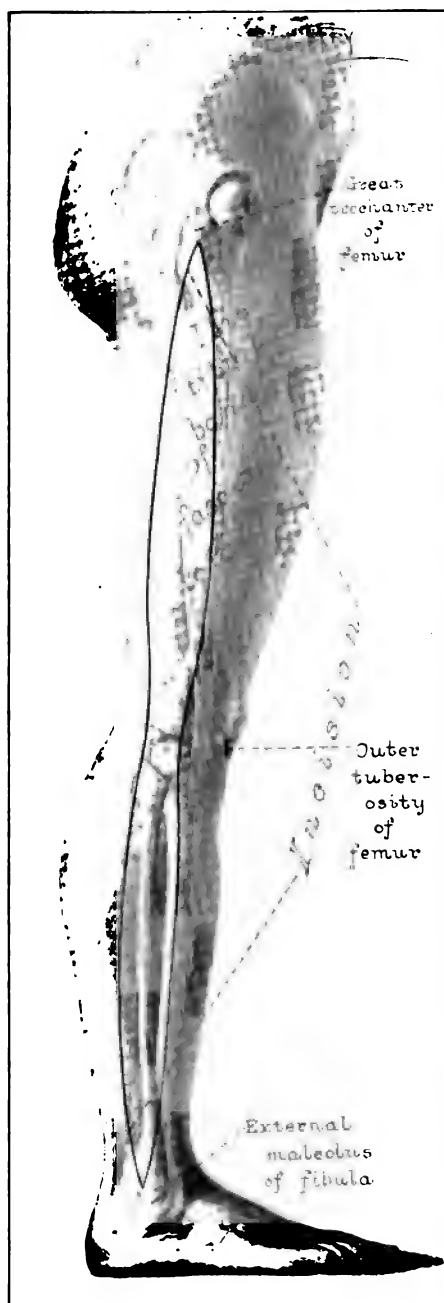


Fig. 387.—Line of incision on the outer surface of the leg and thigh.



Fig. 388.—Line of incision on the inner surface of the leg and thigh.

## EXAMINATION OF TISSUES\*

*Gross Pathology.*—Grossly, the specimens examined presented a reduction in the thickness of the epidermis with a marked thickening of the dermis. A large amount of fat was present underneath the dermis, which was separated into lobules by fibrous connective-tissue trabeculæ. These trabeculæ connected with the aponeurosis, which was also greatly thickened.

*Microscopic Appearance of the Tissues.*—Microscopically there was a reduction in the thickness of the epidermis. The epithelial papillæ were very much diminished in length and, in a number of areas, they had completely disappeared. The dermis showed a marked thickening and fibrosis. The sweat-glands were partially compressed by the excess of

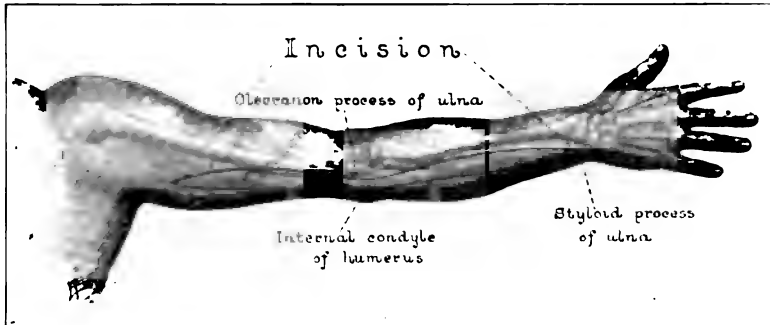


Fig. 389.—Line of incision on the outer surface of the arm and forearm.

fibrous tissue, while the veins and lymphatics were dilated. The elastic tissue of the skin had entirely disappeared. The fibrous trabeculæ which separate the fat lobules and connect with the aponeurosis showed numerous dilated veins, capillaries, and lymphatics, and also small groups of leukocytes. The aponeurosis presented a picture similar to that of the trabeculæ. There were evidences of edema throughout the tissue.

## TECHNIC OF OPERATION

In our first cases we followed as closely as possible the technic, as we understood it, which had been used by Kondoléon. We gradually realized that better results were obtained when a fair amount of hyper-

\*Dr. Broders, of the laboratory of fresh tissue diagnosis, has very kindly done this portion of the work.



trophied skin was removed in addition to an extensive removal of the edematous fat, and that it was necessary, in order to obtain the best results, to remove, as Kondoléon has emphasized, a wide strip of aponeurosis. Since we have practised the removal of the skin we have changed slightly our method of procedure, although we achieve, in the end, results identical, except for a wider removal of skin and fascia, with those obtained in our first cases. At present we perform the operation as follows:

A long modified elliptic incision, which includes the skin to be sacrificed, is made on one side of the affected limb. On the outer aspect of one of the lower extremities this incision would extend from the trochanter to the external malleolus. Then, in order to facilitate a wide removal of the subcutaneous fat, the skin is reflected on each side of the

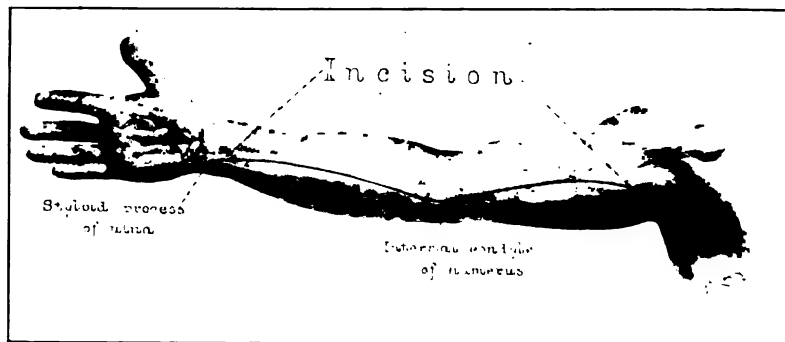


Fig. 390.—Line of incision on the inner surface of the arm and forearm.

incision for a distance of about one or one and one-half inches. The skin is retracted, and underneath each of the reflected skin edges a long incision is made through the edematous subcutaneous fat down to and including the aponeurosis. These incisions are made almost parallel to the original skin incision. Included between them is a quadrilateral piece of edematous fat and aponeurosis. At the upper end these two incisions through the aponeurosis are connected by a transverse incision. The tissues to be removed are now free except for the attachment of the aponeurosis to the underlying muscles. By traction on the tissues that are to be removed it is very easy to dissect the aponeurosis from the muscle throughout the length of the entire limb and to remove in one long piece the skin edematous fat, and aponeurosis. A number of vessels which tend to bleed profusely are encountered. These are temporarily con-

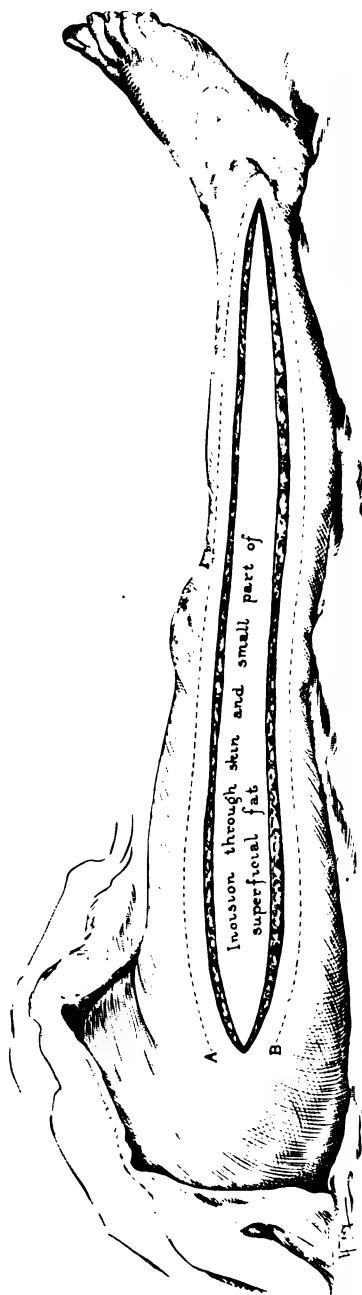


Fig. 391.—Incision used on the outer surface of the thigh and leg. Dotted lines A and B show extent to which the skin is reflected for the removal of subcutaneous fat.

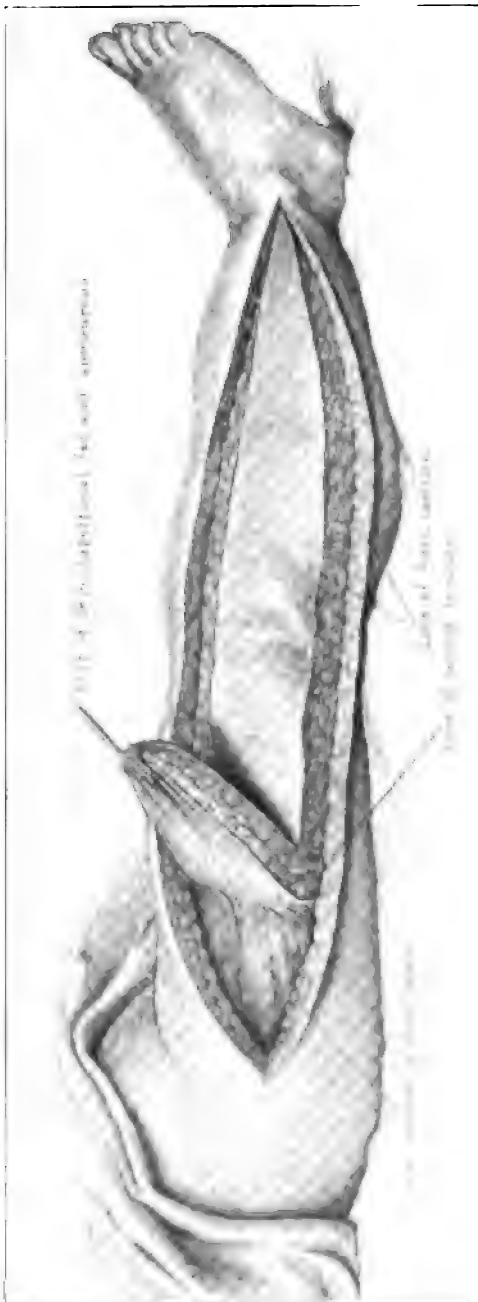


Fig. 392.—Skin, a large amount of subcutaneous fat and aponeurosis removed in one piece.

trolled with forceps. After the tissue has been removed, these forceps are taken off, and surprisingly few of the vessels will be found to need ligatures. The wound is closed with interrupted silkworm-gut stitches.

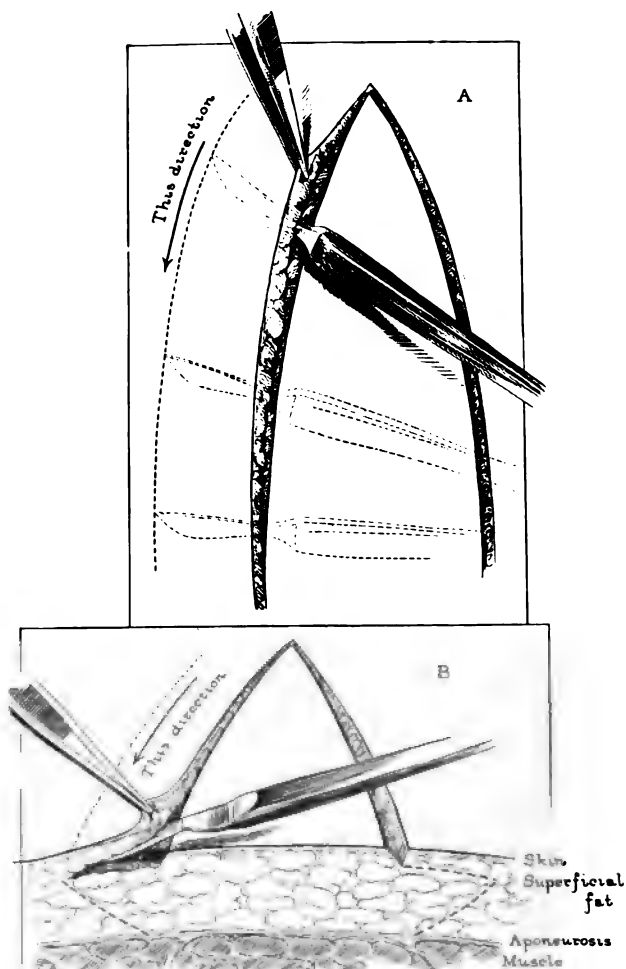


Fig. 393.—*A*, Method used to facilitate the removal of a large amount of subcutaneous fat. After the incision has been made the skin and a small amount of fat are reflected in order that a larger amount of fat may be removed. *B*, Cross-section of *A*.

without drainage. It is necessary to do a similar operation on the opposite side of the limb. If the patient's condition permits, we usually do this as soon as the first operation has been completed; if not, after a period of eight or ten days has passed. The tissues, although diseased,

heal remarkably well, and in none of the cases in which we have operated has there been the slightest infection (Figs. 387-393).

After operation the patient is kept in bed for eight or ten days. An elastic bandage is then applied and the patient allowed to get up and walk about. We have advised the use of this elastic bandage for several months, and if there is a tendency toward swelling when it is removed, it should be worn for an indefinite period. The suggestion of Matas, to administer antistreptococci serum or vaccine at intervals for some time after the operation, has been followed.

Our experience with the Kondoléon operation leads us to believe that in this we have a procedure whereby much aid can be offered to patients suffering with a true elephantiasis, and especially so to those in whom the condition is present in the lower extremities.<sup>1</sup>

#### REPORT OF CASES

CASE 1 (41167).—A woman, aged twenty-one, with the congenital type of elephantiasis of the left leg, which had been present since she was one and one-half years of age, was first seen in the Mayo Clinic at the age of fifteen. At that time there was a tremendous enlargement of the left foot, leg and thigh, and a marked thickening of the skin covering these. In August, 1911, according to Handly's method, one silk strand was placed on the outer and one on the inner aspect of the leg, from the ankle to the region of the left groin. The patient returned six months later without improvement; in fact, the enlargement had increased. In February, 1912, a double silk strand was placed subcutaneously on the outer and inner aspects of the leg, and the inner of these strands was extended upward into the fat of the abdominal wall, while the outer strands were carried as high as the left axillary line. The condition remained unchanged until her return more than four years later. At this time, December, 1916, an operation of the Kondoléon type was done, first on the outer side of the leg, and about one month later, on the inner side. The improvement was marked from the beginning, and at the time of her discharge, in March, 1917, the leg was much smaller than before the operation. A letter received in May, 1918, stated that the leg at present was smaller than when she left here, and that she was able to walk and even to run with but slight inconvenience.

CASE 2 (170799).—A woman, aged twenty, with elephantiasis nostras, presented a history that was negative until she was eleven years of age, when there was a severe infection following vaccination on the left arm. After the vaccination wound healed she was in good condition until two years before coming to the clinic. At this time swelling of the left hand had developed and had slowly progressed until the fore-

arm and arm were involved in the process. She had had many attacks of erythema in the swollen portion. The history and findings in this case have been reported in detail by Elliott. At the time of our examination, July 9, 1917, the patient presented a diffuse swelling of the arm, forearm and hand. The swelling was much more marked in the hand and gradually diminished up to a point a few inches below the acromion process. It also involved the proximal phalanges of the fingers. There

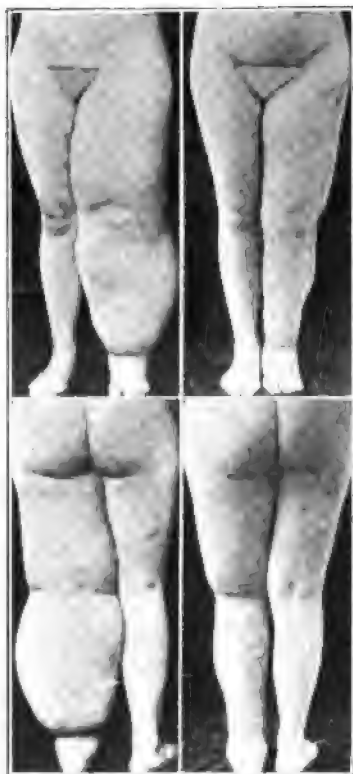


Fig. 394 (Case 1).—Anterior and posterior views before and after operation.



Fig. 395 (Case 6).—Anterior and posterior views before and after operation.

was a definite thickening of the skin. July 13 an operation of the Kondoléon type was performed through incisions 5 or 6 inches long on the anterior and posterior surfaces of the arm and forearm. No incisions were made on the hand. Considerable improvement followed in the arm and forearm, but the condition in the hand remained stationary and some swelling also remained about the elbow. A second operation was done September 29, at which time two incisions were made on the dorsal surface of the hand and one on each of the lateral surfaces of the

elbow. Multiple incisions were also made on each proximal phalanx of the fingers. The arm and forearm have returned practically to normal. Following the second operation there was considerable improvement for a while in the hand; later, however, the dorsal surface of the hand had a return of the swelling and at the present time (June, 1918) it is swollen.

CASE 3 (206558).—A woman, aged fifty-one, had lymphedema of the left arm following amputation of the breast with removal of the axillary

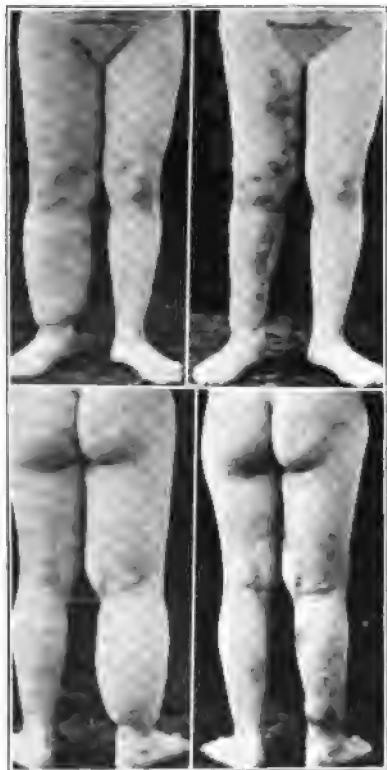


Fig. 396 (Case 5).—Anterior and posterior views before and after operation.



Fig. 397 (Case 7).—Anterior and posterior views before and after operation.

glands, done elsewhere. The wound had not been infected. Two months after the operation the arm began to swell, growing slowly but progressively worse and involving the dorsal surface of the hand, the forearm and the arm nearly as high as the shoulder-joint. There was no thickening of the skin. Sept. 1, 1917, a Kondoléon type of operation was done. Long incisions were made on the outer and inner aspects of the arm and forearm from a point a few inches below the shoulder-joint down to the

wrist; also two incisions were made on the posterior surface of the hand. The swelling in the hand decreased at once, and there was marked improvement in the arm and forearm for a time. A recent letter (May, 1918) would lead us to infer that there is slightly more swelling at this time than there was when she was discharged from our care. This, however, is of a fluctuating character, and is less at times.

**CASE 4 (216446).**—A woman, aged forty-three, with an elephantoid condition of the left forearm, had a fall down stair-steps two years before being seen in the clinic, with injury to the left forearm. Three days later the skin on the outer surface of the forearm became red and then black, and remained so for two or three weeks. Three months later the forearm swelled and remained so until she was examined here in January, 1918. At times there was also swelling on the dorsal surface of the hand. When seen, the patient was found to have a swelling of the left forearm, with considerable thickening of the skin. January 12 an operation of the Kondoléon type, similar to the one described in the previous cases, except for the fact that no incisions were made on the dorsal surface of the hand, was done. There was marked immediate improvement which persisted until April 1. The patient, in a recent letter, states that at this time the forearm from the elbow to the wrist became inflamed and full of red blotches. Following this the swelling returned, and at the present time (June, 1918) the arm has been swollen for two months. She states that the swelling is nearly as marked now as before the operation.



Fig. 398 (Case 2).—Three months after Kondoléon operation. Unfortunately, no photograph was taken in this case before the operation.

**CASE 5 (213799).**—A girl, aged seventeen, had a negative history until 1912. At that time the right leg became swollen without apparent cause and remained so until she was seen here in November, 1917. No etiologic factor could be obtained. The patient had septic tonsils, which were removed after her operation. When examined, there was a very marked enlargement of the right leg and thigh, with thickening of the skin. An operation of the Kondoléon type was done Nov. 27, 1917. It was followed by marked improvement, which has been permanent to the present time (June, 1918).

**CASE 6 (221137).**—A girl, aged twelve, when three and one-half years of age, developed swelling on the inside of the right knee, which was followed by a swelling of the leg and thigh. The condition began one month after an attack of measles. She consulted us in February, 1918, at which time there was fairly marked swelling of the leg and

thigh, with considerable thickening of the skin. She also had a tuberculous synovitis of the right knee-joint, with slight effusion into the joint, and a tuberculosis of the right inguinal glands. A Kondoléon operation was done Feb. 12, 1918. This was followed by a very fair decrease in the size of the limb, which has remained stationary to the present time (June, 1918). The result following the operation in this patient was not quite so good as that obtained in the other patients in whom the condition was present in the leg.

**CASE 7 (228071).**—A woman, aged twenty-one, five and one-half years before she was seen in the Mayo Clinic, in 1918, developed tonsillitis which was followed by an arthritis with fever. At the same time there were several large boils on her face and right arm. Two and one-half years later the patient developed an amenorrhea, and during six

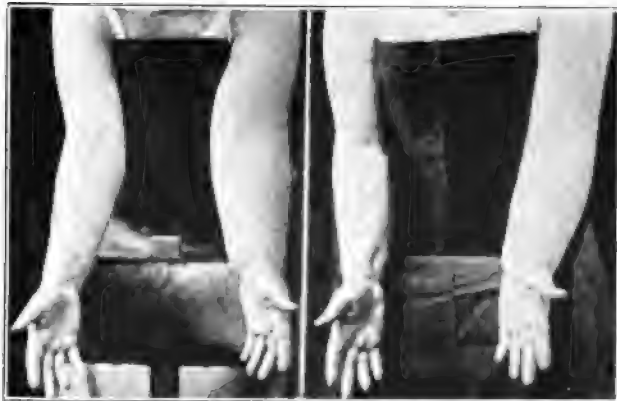


Fig. 399 (Case 3).—Arm before operation and two and one-half months after operation.

weeks' time lost 30 pounds in weight. She was then told by her physician that she was anemic. The swelling in the right leg continued up to the date of her visit to this clinic, when there was a marked edema of the right leg, with considerable thickening of the skin. A Kondoléon operation was done on one side of the limb April 20, and on the other side, April 30, 1918. It was followed by immediate and very marked improvement which has continued up to the present time (two months). In this instance the limb returned practically to a normal state.

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## RECURRING INGUINAL HERNIA\*

J. C. MASSON

No surgical procedure is more uniformly satisfactory than that of the operation for the radical cure of inguinal hernia. This is undoubtedly due to the fact that at least nine of ten cases are of the indirect type and hence favorable for surgery.† Probably about 75 per cent of all indirect inguinal hernias are the result of a persistent congenital sac without any other congenital abnormality or atrophy in the regional tissues.

It is unfortunate that in most published statistics the distinction is not more clearly drawn between the various types of inguinal hernia, since the one type, and fortunately the most common one, is readily cured by almost any form of operation, providing that an obstruction is placed in the neck of the sac at the level of the internal ring. This can be accomplished by ligation, compression by the tight closure of the canal, or plugging from the inside, as is occasionally attempted by pseudo-surgeons who inject paraffin. On the other hand, the direct inguinal hernias, the large scrotal hernias of long standing of whatever type, the so-called sliding hernias, and the recurrent hernias are satisfactorily treated by some form of plastic closure of the inguinal canal as well.

I wish to emphasize the vast difference in the curability by operation of the various types of inguinal hernia, and to urge the advisability of using some form of transplantation of the cord or a plastic closure of the floor of the inguinal canal in at least all the difficult cases. Personally, I believe that a technic which is preferable in difficult cases is also preferable in simple cases. The additional few minutes required and the satisfactory results obtained in every respect make the more radical operation advisable in practically all cases. Our own statistics in 7016 cases (this includes 1652 cases reported by Judd in 1907) show a little less than 1 per cent of recurrence following the cord transplantation, and a little

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† Davis, in a splendid report of the end results in 1500 cases operated on in the Massachusetts General Hospital, reports 94.2 per cent indirect and 5.8 per cent direct.

more than 1 per cent following the anatomic operation. In Coley's statistics the difference is even more marked, with 0.6 per cent of recurrence following the Bassini operation and 4 per cent following the Ferguson operation.

Five thousand three hundred sixty-four inguinal hernias have been operated on in the Mayo Clinic from 1907 to the first of this year (1918). Two thousand two hundred thirty-four were right inguinal hernias, 1430 left inguinal, and 850 bilateral inguinal. Three hundred thirty of the operations were done for recurrence; 260 for recurrence following operation done elsewhere, 70 following operations in the clinic. This included 29 bilateral recurrences, which were counted as 58 operations. Two hundred fifty-eight of the 330 patients with recurrence had had one previous operation, 44 had had two, 20 had had three, and 8 had had four. These figures show distinctly that the more frequent the previous operations, the greater the difficulty in securing a radical cure, as the number of cases in which two or three operations are required must be very small. In many instances it is difficult to determine from the history the type of operation that has been done and where the recurrence has taken place, but experience with these cases seems to demonstrate that by far the greater number follow the so-called anatomic or Ferguson type of operation, especially when it has been used in the direct hernia.

Inguinal hernias are believed by the laity, and by many members of the medical profession, to be all of the same type and readily curable if properly operated on. This is an unfortunate impression. The patient should be prepared for the possibility of a recurrence, or, on the other hand, he should be told that the hernia is a simple one and that he has a little better than 99 chances out of 100 for a perfect result if a careful pre-operative examination is made. The hernias that are particularly difficult to cure are those, either direct or indirect, that are associated with a poorly developed internal oblique muscle, and this type can always be determined by a digital examination through the external abdominal ring. The normally developed internal oblique and conjoined tendon, when it is present, can readily be felt, and the distance between these structures and Poupart's ligament accurately estimated. In the other cases the reverse is true, and in the worst cases no resistance is encountered until the edge of the rectus is reached. Erdman (1917), in a review of 148 cases, found that there were but two recurrences in 102 indirect inguinal hernias, and no less than 7 recurrences of 46 of the direct type.

Another hernia difficult to cure, and yet which belongs to the indirect type, is the one so often found in old men who have a hernia of long standing with a large mass of omentum or omentum and bowel descending into the scrotum, and who have probably worn a truss for many years with complete satisfaction until the last few months. In these cases the deep epigastric vessels are drawn down almost to the crest of the pubes, and the internal abdominal ring is directly behind the external abdominal ring, with marked enlargement of both rings, and the surrounding tissue is of a very poor quality for plastic work.

The direct-indirect, saddle-bag, bilocular, or pantaloon hernias, as they are variously called, present no difficulties that are not common to all direct hernias, except that it is also necessary to remove the part of the sac that accompanies the structures of the cord, as well as to treat that portion which comes through the transversalis fascia below the deep epigastric vessels.

The operation for sliding hernia is always difficult on account of a large internal ring, and after the removal of as much of the sac as possible the bowel still protrudes, and when returned into the abdomen tends to make a direct and constant pressure on the line of closure of the inguinal canal.

Operations on recurrent ruptures invariably present added difficulties, as a rule, increasing with the number of previous operations. It is not at all uncommon to find a direct hernia at the second operation when the surgical findings at the first operation indicate that an indirect sac was removed at that time. These hernias are always associated with a poorly developed internal oblique muscle, and in most cases are the result of injury to the nerve supply of the lower fibers of the muscle.

#### AGE INCIDENCE

Under 20 years . . . . .	8 cases (2.4 per cent)
20-30 years . . . . .	69 cases (20 per cent)
30-40 years . . . . .	80 cases (24.1 per cent)
40-50 years . . . . .	88 cases (26.3 per cent)
50-60 years . . . . .	59 cases (18 per cent)
60-70 years . . . . .	21 cases (6.4 per cent)
Over 70 years . . . . .	9 cases (2.8 per cent)

In the 330 cases of recurrence only 8 patients were under twenty years of age, and all gave a history of recurrence having taken place immediately following the first operation. None of these 8 patients had been operated on by us and, therefore, we have no record as to the type of the hernia at the time of the first operation. It is an interesting fact

matter to reduce the contents and free the sac from the normal cord structures (Fig. 401). If firm adhesions are encountered, rather than to traumatize the cord structures or leave an extensive raw surface, which would ooze considerably afterward, I prefer to cut the sac close to its neck, and if the cut end of the distal section is left open, it will not lead to future trouble. The proximal portion may then be treated in the ordinary manner. Any preperitoneal fat tags accompanying the cord structures through the internal ring should be ligated as high as possible

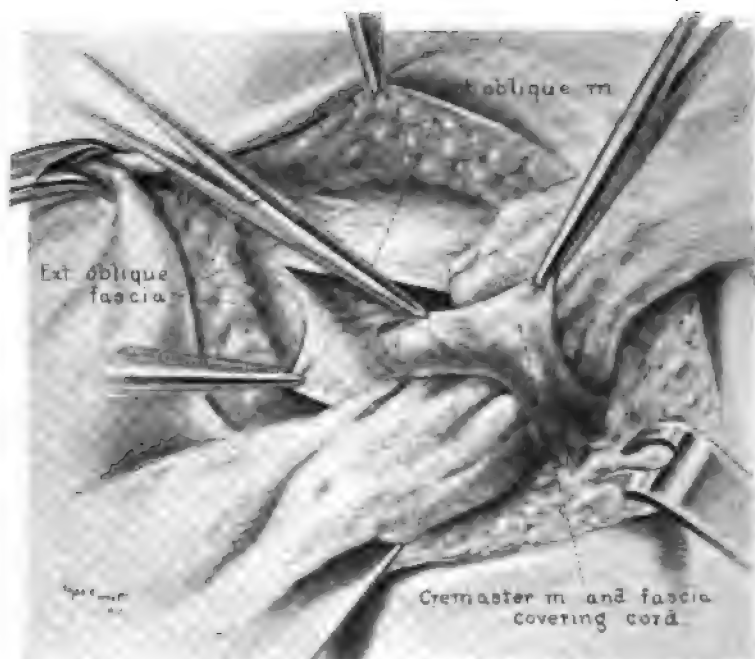


Fig. 400.—Spermatic cord freed throughout the entire length of the inguinal canal. Coverings of cord held with forceps.

and excised. It is important to handle the cord structures as little as possible, in order to avoid postoperative pain and swelling.

The neck of the sac is thoroughly freed from the edge of the cremaster and transversalis fascia and ligated at as high a point as possible; the stump is transfixed to prevent the slipping of the ligature, and the distal portion is cut off. The free end of the ligature used for tying the sac is then threaded onto a large hand needle, and by this is carried through the transversalis and the internal oblique muscles, as shown in Fig. 401.

at a point about  $1\frac{1}{4}$  inches above the internal abdominal ring. By drawing the neck of the sac tightly up to this point and fixing it there by

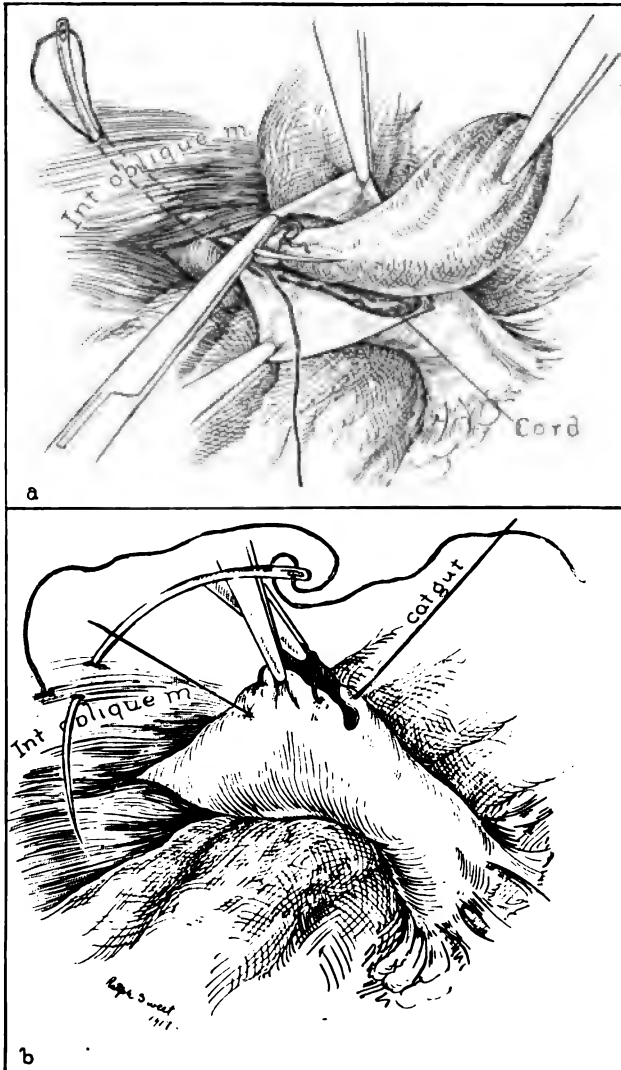


Fig. 401.—a, Hernial sac isolated; neck ligated and suture carried through the internal oblique above the internal ring. b, Sac excised, closure of cremaster preliminary to fixing the neck of the sac well above internal ring.

tying the catgut, the sac is prevented from causing pressure at the internal ring while healing is taking place. This procedure carries out

the Kocher idea, and is a much safer and simpler method. The opening in the cremaster is now closed, and the cord is held out of the way by a piece of gauze while the canal is closed (Figs. 402 and 403). In the cases of direct hernia, unless the sac is large, it is not opened but simply turned in, with its covering of preperitoneal fat, and a few stitches placed in the base to prevent it from making pressure on the suture line during the process of healing. I have been more particular in this respect since having opened into the bladder in one such case. However, the accident

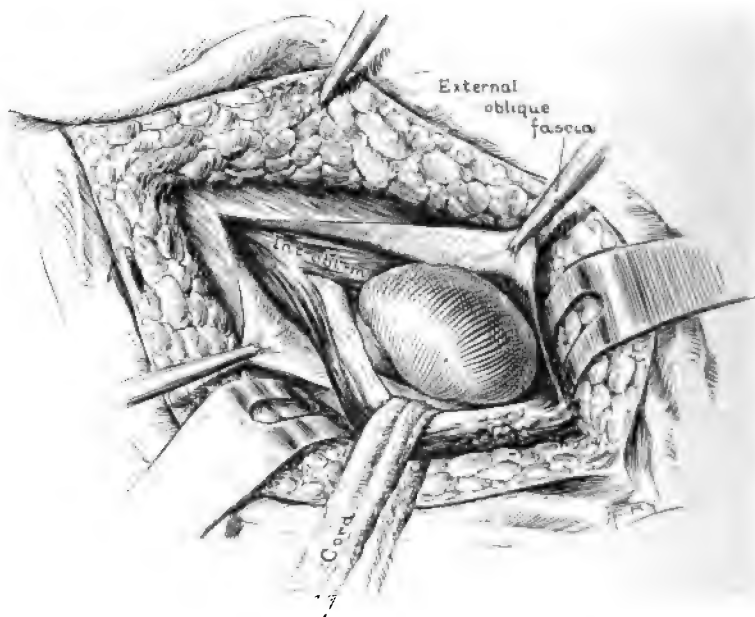


Fig. 402.—Direct inguinal hernia.

was recognized at once and satisfactory closure was made, the wound healing without drainage.

The plastic closure of the inguinal canal is the most important step in the prevention of recurrences in direct hernias and in all the difficult cases of the indirect type (Fig. 404). The principle generally credited to Bassini, of bringing the internal oblique and conjoint tendon down to Poupart's ligament behind the spermatic cord, would probably be sufficient in all cases in which these structures are well developed and the interval between them is not too great. However, additional security is obtained by bringing the cut edges of the external oblique aponeurosis down to Poupart's ligament also, as first suggested by Halsted (Figs.

405 and 406). Additional strength is also obtained by the Andrews imbrication of the external oblique, which, in addition, makes a covering for the cord.

Marked atrophy of the internal oblique is often seen in recurrent cases or when patients have worn a truss for a long time. In such cases it is frequently advisable to utilize either the sheath of the rectus or the rectus muscle itself. I prefer the latter, and by freely slitting up the

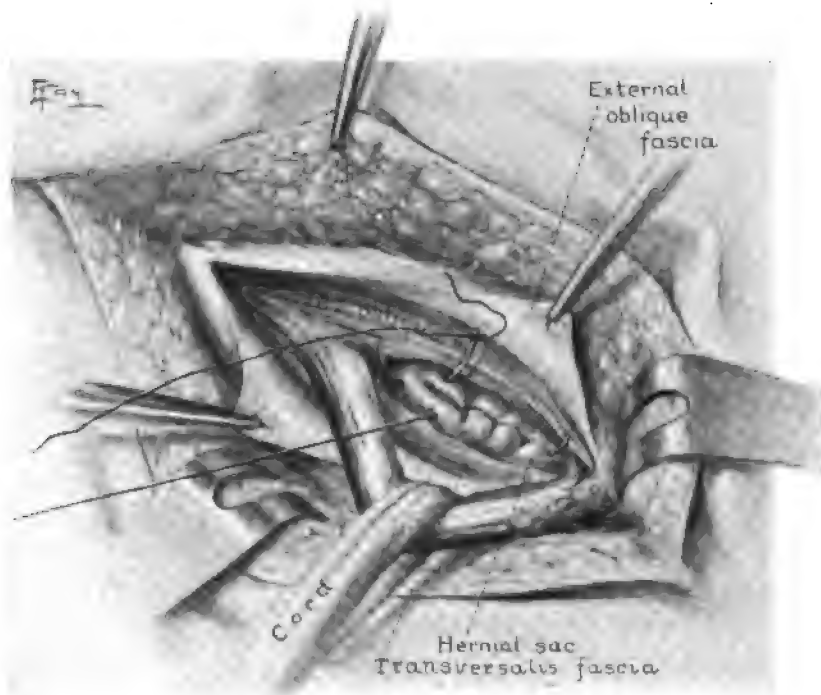


Fig. 403.—Sac of direct hernia inverted without removing any of it and the base with adherent preperitoneal fat sutured.

sheath (as a rule, about three inches), it is always possible to draw the muscle-fibers down to Poupart's ligament without undue tension. In most cases of this type it is advisable to follow Bloodgood's suggestion of cutting the sheath of the rectus posterior to the attachment of the internal oblique, and in this way the use of that muscle in strengthening the closure at the internal ring is not interfered with.

The suture material is of the utmost importance, and the use of



heavy absorbable and non-absorbable material is more frequently an added danger than a safeguard against recurrence. The mistake so often made, and frequently hard to guard against, is making the closure under too much tension, with the result that the sutures cut through or strangulate the tissues and a recurrence results. Once healing is secure, non-absorbable material remains as a foreign body in the wound and is a weakness rather than a strength.

The closure is started at the bottom of the canal, the first stitch going

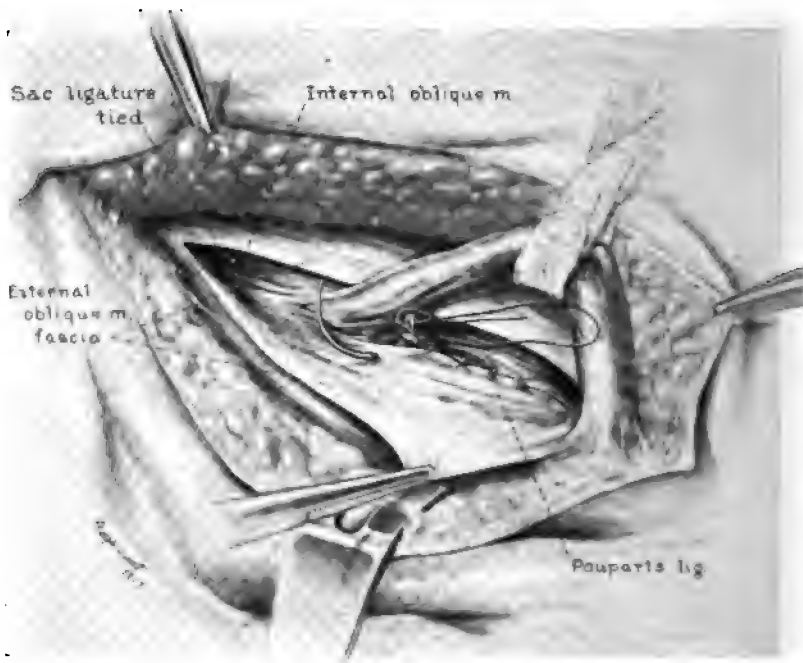


Fig. 404.—Conjoined tendon and internal oblique sutured to Poupart's ligament with continuous chromic catgut.

through the internal oblique (or conjoined tendon when present) close to its insertion into the crest of the pubis, and Poupart's ligament near its insertion into the spine of the pubis. When this suture is tied, the structures almost approximate one another throughout the entire length of the inguinal canal, and no tension is required to complete the closure by whipping the internal oblique to Poupart's with about six stitches. A fairly tight closure should be made at the internal ring, making sure that there is little danger of constriction of the cord at this point, especially

when the natural coverings of the cord are preserved. Fig. 405 shows the upper layer of the aponeurosis of the external oblique being drawn down to Poupart's and, as there is a little extra tension at the upper outer end, an extra stitch may be inserted at this point by tying the free end of the ligature. The approximation of the external oblique to Poupart's is then completed with the continuous suture, which is finished at the spine of the pubis and tied to the free end at that point.

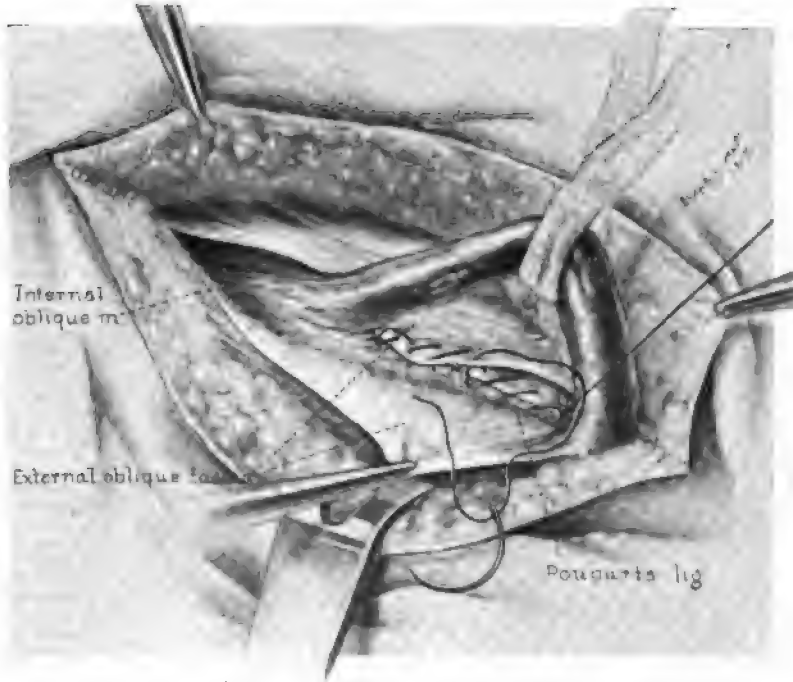


Fig. 405.—Upper layer of external oblique sutured to Poupart's ligament.

As an occasional point of recurrence of the hernia is directly above the cord where it emerges through the internal ring, I follow Coley's suggestion and put one stitch in the internal oblique and Poupart's at this point, being careful not to injure the ilio-inguinal or the iliohypogastric nerves, which lie on the surface of the muscle (Fig. 407). Continuing with the same suture, one or two stitches are generally placed in the external oblique above the cord, imbricating the lower part on top of the upper, continuing down and inclosing the spermatic cord structures between two layers of the external oblique aponeurosis, as shown in Fig. 406.

Hemostasis is very important, and after tying all visible bleeding vessels the space between the skin and the external oblique is obliterated as nearly as possible by closing the subcutaneous tissue with a continuous plain No. 1 catgut suture, and by making frequent catches into the surface of the external oblique. It is not necessary to use tension stitches, and I prefer to close the skin with continuous horsehair.

A light gauze dressing is applied, and a suspensory bandage put on the scrotum. Most of the postoperative pain and swelling are due to

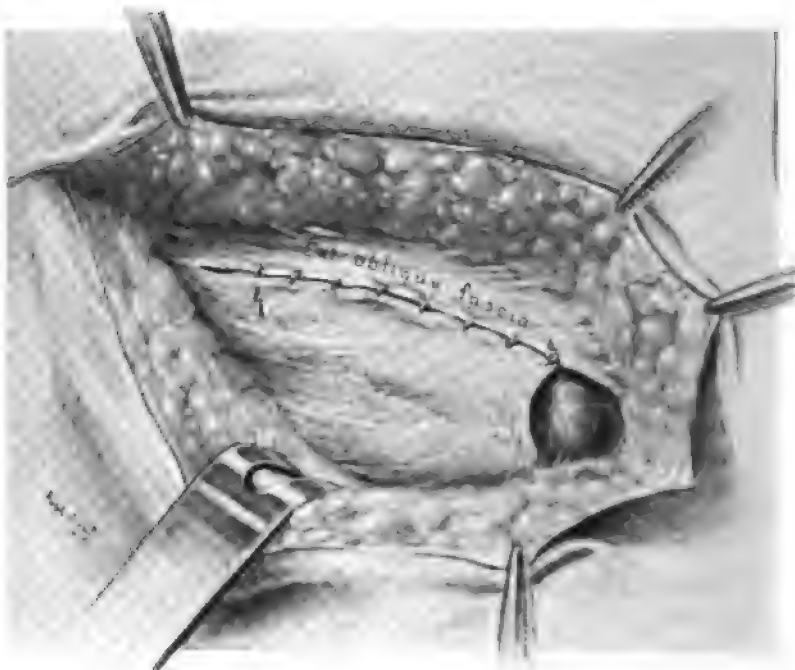


Fig. 406.—Cord structures covered with the lower layer of the external oblique aponeurosis.

oozing or unnecessary handling of the cord structures and testicle. I do not believe it is ever necessary to deliver the testicle from the scrotum unless the patient has a co-existing pathologic condition of that organ.

The majority of patients are allowed to get up on the eighth day, but in the worst cases, including all recurrent hernias, the patients are kept in bed about fourteen days. Light work is allowed in from six to eight weeks, and heavy work in from three to six months.

In our 256 cases of recurrences in which the time of recurrence was

recorded, 189 recurred in the first six months, 26 recurred between six and twelve months, 19 recurred between one and two years, and 22 recurred between two and eight years.

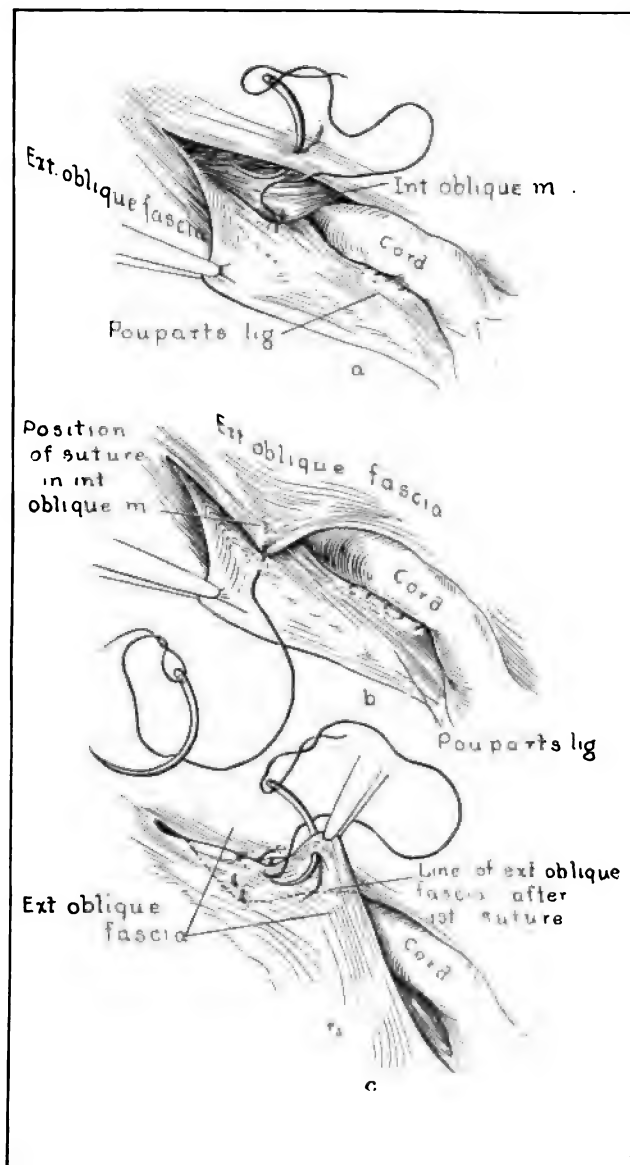


Fig. 407.—Internal and external oblique sutured to Poupart's ligament above the level of the internal abdominal ring.

If a hernia recurs within six months, either the operation was not sufficient or the patient overexercised after operation. On the other hand, recurrences after twelve months are more apt to be due to the development of a new hernia as the result of stretching in scar tissue or atrophy in the muscles. One cause for this is, without doubt, the wearing of trusses following operation, and another cause is injury to the ilio-hypogastric nerve, with resulting atrophy in the internal oblique, which frequently occurs at the time of the first operation, and, as Balfour has shown, may also be the result, when on the right side, of a gridiron incision for appendicitis.

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## THE TREATMENT OF MENORRHAGIA WITH RADIUM\*

LEDA J. STACY

Menorrhagia occurs more often at the beginning and at the ending of the menstrual function. It is seldom that the profuse menstruation of the first decade of menstruation is due to a demonstrable lesion, but rather to defective uterine musculature or, more probably, to a disturbance in the balance of the internal secretions. The inter-relationship of the functioning of the glands of internal secretion opens up a most interesting field for study. The secretions of the adrenal medulla and the thyroid have been studied quantitatively because the active constituents of these two glands have been separated as pure chemical compounds.<sup>6</sup> That the other ductless glands also furnish secretions which contain physiologically active substances is undoubtedly true, but as yet these secretions have not been isolated in a form in which they can be studied quantitatively and their exact action determined.

The menorrhagias of the second and third decades may occur, with no gross lesions apparent, in cases of polypoid endometritis and sometimes as a result of passive congestion in a retroverted or a prolapsed uterus, or, occasionally, as a result of chronic pelvic infection; but the most frequent cause of hemorrhage at this period is the presence of a uterine myoma, of polyps, or of carcinoma.

Hypertrophic endometritis is not now considered a definite pathologic condition of the endometrium, but a normal physiologic congestion of the menstrual cycle.<sup>3</sup>

The management of the profuse menstruation in those cases in which no gross lesion is found, or in cases in which a small myoma exists, has not, in the past, been especially satisfactory. In some instances young persons respond to glandular medication, such as ovarian and thyroid extract and pituitrin. A few patients have improved after blood trans-

\* Presented before the Southern Minnesota Medical Association, Winona, June, 1918. Reprinted from *Minn. Med.*, 1919, ii, 88-92.

fusion and following the use of horse-serum, but the effect, as a rule, has been that of temporary relief only. Curetment is seldom effective and should be tried only after medical treatment has failed. This type of menorrhagia, in older persons, has usually been treated by local medication and repeated curetments.

In many of the cases in which a small myoma is found, the conservative surgeon hesitates to submit the patient to so radical a procedure as a hysterectomy, or even to a myomectomy.

The work of Wickham showed that the beta and gamma rays of radium produced an endarteritis, which goes on to the obliteration of the blood-vessels. This fact led Abbe, in 1905, to make the first use of radium within the uterine cavity to control bleeding, in a case of fibroids in a patient forty-nine years of age.

The effect of the gamma rays on the ovarian tissue is still a contested point. Horowitz has shown experimentally that in two to three days following exposure to the x-ray and to the gamma rays of radium the nuclei of the mature Graafian follicles break down, and in ten days the follicle is almost entirely destroyed, thus preventing the development of the corpus luteum. Kelly and Burnam consider that the decrease in the size of the fibroids and the cessation of the hemorrhage are due to the anemia following the obliteration of the blood-vessels. They cite cases in which fibroids have appeared after the menopause or after the removal of the ovaries. They also report two cases in their series in which the fibroids disappeared without cessation of menstruation.

Radium was first used in the Mayo Clinic about three years ago (1915) in the treatment of menorrhagia of the menopause in cases which presented no gross pelvic lesion, and in those presenting a fibroid, but with contraindication to operation. Since then the types of cases treated have been increased, and now radium is considered the treatment of choice in all cases of the menorrhagia of menopause in which the presence of carcinoma is definitely excluded, either by history or by a diagnostic curetment, and in those cases not presenting a large, soft myoma, which is apt later to undergo degeneration. The radium is also used in cases of profuse menstruation of the young woman—(1) When there is a small submucous fibroid; (2) when no gross pathologic condition is demonstrable; and (3) in cases presenting a large myoma in which there is a definite surgical risk.

However, we have not entirely replaced myomectomy with radium for the treatment of myomas in the patients between the ages of thirty

and forty years. In a series of 510 abdominal myomectomies for uterine myomas done in the Mayo Clinic from January, 1898, to January, 1918, there have occurred 23 full-term pregnancies and 1 miscarriage. Seven women were pregnant at the time of answering the questionnaire, making a total of 31 (12.3 per cent) pregnancies occurring after myomectomy. I have found in the literature but one case of pregnancy going to full term following radium treatment, and in our series there was one case of miscarriage with a dead fetus at seven months. Therefore, in most cases of myoma during the child-bearing period myomectomy is the procedure of choice.

Of the 175 patients that were treated with radium from August, 1915, to December, 1917, there were 2 under twenty years of age (1 was fifteen). There were 34 from twenty-one to thirty years; 45 from thirty-one to forty; 91 from forty-one to fifty; and 14 were more than fifty years of age. Of this number, 93 had had previous curetments, 37 had had more than one curetment, and 56 had undergone other pelvic operations. In 69 cases there were complications that were considered as relative, though not in every instance absolute contraindications to operation. There were heart lesions in 34 cases, hypertension in 8, kidney lesions in 11, obesity in 8, and pulmonary tuberculosis in 6. Hyperthyroidism occurred in 2 cases. Seventy-seven of the 175 patients had definitely palpable fibroids. In 82 instances the uterus was classified as large, and in 45 it was definitely stated that the uterus was not large. It is interesting to note that 155 of the 175 patients were married women, and that of these only 25 had not been pregnant.

#### TREATMENT

The technic used by us is similar to that in use elsewhere. The patient is given a cleansing douche, the cervix is drawn down by a tenaculum forceps, swabbed with tincture of iodine, and gently dilated, and the radium is inserted into the uterine canal. The radium element is encased in a glass tube within a silver tube 0.5 mm. thick, and this in turn is inclosed in a rubber tube 0.5 mm. in thickness. This screening is sufficient to filter out the alpha- and the soft beta-rays which produce the local irritation. A narrow strip of plain gauze is carried into the cervix and the vagina is packed.

The patient is allowed to leave the hospital a few hours after the radium is removed. She keeps off her feet for the following twenty-four hours. If there has been a recent hemorrhage, or if the treatment is



given during the menstrual flow, the patient remains in bed until the flow ceases. Usually the flow at the first period after the treatment is as profuse as usual, or it may be increased in amount. The reason for this is not definitely known. It may be because of the local hyperemia of the endometrium, produced by the beta-rays, or it may be due to the liberation of the ovarian hormone by the destruction of the corpora lutea.<sup>2</sup>

In the majority of patients more than forty-five years of age, and in all in which there is intermenstrual bleeding, a diagnostic curetment is done previous to the radium treatment. If the clinical history is at all suggestive of a carcinoma of the fundus, a hysterectomy is done, for even a very thorough curetment may fail to reveal a carcinomatous focus.

The dosage of radium is gaged by the age of the patient and by the presence or absence of a tumor. In the young person without a demonstrable tumor, and when it is desirable to continue menstruation, usually one application of 50 mg. of radium element for from four to six hours (200 to 300 mg. hours radium) is used. In older persons in whom it is desirable entirely to stop menstruation it has been found that an exposure of 50 mg. for from ten to twelve hours has brought about the desired results. In cases in which large dosage is used menstruation is usually irregular for about two months and ceases entirely after the second or third month; following the lighter exposures it becomes regular and normal in most instances in about two months. It is our custom not to repeat the treatment until an interval of three months has elapsed. If, after that time, menorrhagia continues, a second treatment is given, and, with the exception of one case, the second treatment has been effective. In this instance menstruation ceased for one year, and then became profuse and the periods prolonged. It has been necessary to give a second treatment in 10 instances in this series. In 8 instances a hysterectomy was done later; 1 elsewhere one month after the radium treatment. One only of these 8 patients had been given a second radium treatment.

Included in this series is one case of adenomyoma of the uterus in which a microscopic diagnosis was made at the time of the exploratory incision. There were one intra-uterine treatment and four abdominal treatments with entire disappearance of the tumor, which at the time of the exploration was the size of a grape-fruit and adherent in the pelvis. At the last examination the uterus was the size of the thumb.

Reports have been received from 143 of the 175 patients, and in 55 (38.5 per cent) menstruation had ceased, not to return to the date of the report; in only 14 did the menstruation cease immediately following the treatment. In 15 menstruation ceased for three months and returned; in 29 (20.2 per cent) the menstruation became normal; in 42 it was reported as regular but somewhat profuse, and in 30 (20.9 per cent) it became profuse. Ninety-two patients report their condition as improved and 27 as not improved. Two died, and in one of these cases the physician reported that death was clinically due to carcinoma before treatment. There had been negative curetment. The second died of pulmonary tuberculosis which existed at the time of the treatment.

#### CONCLUSIONS

Radium is the treatment of choice in:

1. Cases of menorrhagia of menopause not associated with large fibroid tumors, and in which the possibility of carcinoma is definitely eliminated.
2. Cases of menorrhagia in patients between the ages of thirty-five and forty years who have small submucous fibroid tumors, or who have no demonstrable lesions.
3. Cases of myomas in which there is a condition making a definite contraindication to operation.
4. Cases of menorrhagia in the young person who has resisted all medical treatment in which very small dosage should be given.

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## **GENERAL**

# PROPHYLACTIC INOCULATION AGAINST RESPIRATORY INFECTIONS DURING THE PRESENT PANDEMIC OF INFLUENZA

## Preliminary Report\*

E. C. ROSENOW

In attempting to lessen the incidence and to reduce the severity of infections of the respiratory tract by vaccination it is essential to consider the wide range of bacterial flora, the relative prevalence of each species, as well as the fluctuations in incidence and severity of these infections with changes in season. The well-defined tendency of bacteria of the same species to localize differently in different epidemics indicates peculiar infecting and antigenic powers. The short duration of immunity to infections following attacks adds greatly to the difficulty. However, owing to the high incidence and high mortality rate from infections of the respiratory tract during the present epidemic, a painstaking effort to raise the resistance of individuals by inoculation with appropriate vaccines appeared to be strongly indicated.

In considering prophylactic inoculations in this epidemic of influenza we put aside the debated question as to the cause of the initial symptoms, and considered primarily the possibility of immunizing persons against the bacteria, pneumococci, streptococci, influenza bacillus, and staphylococci, which are conceded by all to be the common causes of death in this disease. It was thought that it might be possible to raise to some degree, by artificial means, the immunity of persons to these microorganisms to which they appear so susceptible, and thus to lower the incidence of the more serious respiratory infections, particularly pneumonia.

The bacteria found as the cause of the complications in this epidemic appear to have exalted and peculiar infecting powers. The mode of death and the findings in the lungs, for example, in the so-called acute bronchopneumonia following influenza, are quite unique and are strik-

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ingly similar irrespective of the species of microörganism present. Infection of the lung by hemolytic streptococci without empyema and without tonsillitis indicates peculiar localizing power of this micro-organism. The influenza bacillus appears to have acquired peculiar virulence. The frequency of staphylococci in the sputum and lung associated with pneumococci and streptococci far exceeds that which occurs in lobar pneumonia. A study of the various strains isolated has revealed commonly marked variations in cultural and other properties. Owing to these findings it was the plan to prepare the vaccine not from saprophytized laboratory strains, as is too often the rule in vaccine therapy, but from strains freshly isolated from the sputum and lungs, and to incorporate the bacteria in the vaccine in about the proportion in which they are found, and before the more or less peculiar properties disappear. A bacteriologic study, made during the progress of the epidemic, showed a decided change in the bacterial flora, and hence new strains were added from time to time in order that the vaccine might represent as nearly as possible the bacterial flora of the disease at various stages of the epidemic.

Heretofore lobar pneumonia has been unusually prevalent for some months following epidemics of influenza. It was felt that this would be particularly apt to be the case following the present epidemic, since it began early in the season. It was decided, therefore, to include a series of the fixed types of pneumococci in the vaccine, although they were infrequently isolated, especially during the early part of the epidemic.

A study of the secretions from the nose and throat, of the sputum and lung exudate, from the very beginning of the epidemic as it occurred in and about Rochester, revealed commonly, among other bacteria, a streptococcus having some distinctive features. Smears from the nose, throat, and sputum at the onset of the attack show quite constantly large numbers of this organism in the form of Gram-positive lanceolate diplococci occurring singly, but more often in rather long chains. The epithelial cells are frequently found packed with this microörganism. On artificial cultivation of these exudates it presents morphologic and cultural features both of the pneumococcus and of *Streptococcus viridans*. It produces on isolation a rather moist, spreading, non-adherent, greenish colony on blood-agar plates and a diffuse cloud in glucose broth. On solid mediums it grows as a lanceolate diplococcus of quite uniform size, and usually is surrounded by a distinct capsule. In glucose broth it produces lancet-shaped diplococci in rather long chains. Smears from

the older cultures often show extreme variations in size and shape. Injection of sputum into guinea-pigs is usually followed by death from peritonitis, the peritoneal exudate and blood showing this organism in pure or almost pure form. It is more virulent than the green-producing streptococci from the throats of normal persons, but is less virulent than pneumococci from lobar pneumonia. The strains do not usually ferment inulin. It does not autolyze readily and is not soluble in bile. Owing to these findings the vaccine was made to contain a heavy mixture of these strains.

The organism is undoubtedly the one found by the English investigators and designated by them as diplostreptococcus, and the one found by Mathers and for which Tunnicliff finds an increased opsonic content in the serum of convalescent patients. Immunologic and other studies to determine further the relations of this organism to influenza are under way and will be reported later.

Hemolytic streptococci were found next most frequently, particularly in fatal cases during the first half of the epidemic. *Staphylococcus aureus* and influenza bacilli appear to play a minor but definite rôle in the production of the complicating pneumonia in some cases. Hence examples of strains of hemolytic streptococci, staphylococci, and influenza bacilli were included in the vaccine.

#### PREPARATION OF THE VACCINE

The formula of the vaccine used during the earlier part of the epidemic, and used exclusively in the cases in this report, is given in Table 1.

TABLE 1.—FORMULA OF VACCINES

Pneumococci—Types I (10 per cent), II (14 per cent), and III (6 per cent).....	30 per cent
Pneumococci Group IV and the allied green-producing diplostreptococci described.....	30 per cent
Hemolytic streptococci.....	20 per cent
<i>Staphylococcus aureus</i> .....	10 per cent
Influenza bacillus.....	10 per cent

The bacteria were grown for from eighteen to thirty-six hours at from 33 to 35 C., in 0.2 per cent glucose broth. The broth was autoclaved at 20 pounds pressure for from one to two hours to insure freedom from living spores. The glucose was added in a sterile manner from a concentrated sterilized solution in water. It was found that the cultures of pneumococci and streptococci yielded approximately 1000 million bacteria and *Staphylococcus aureus* 2000 million bacteria per cubic centi-

meter. Luxuriant growth (about 1000 million per cubic centimeter) of the influenza bacillus was obtained by adding approximately 1 c.c. of laked human blood per liter of glucose broth. The strains were grown separately in the flasks. Smears were made before centrifugation of each flask to eliminate possible contaminations. The pneumococci and allied green-producing streptococci, the staphylococci, and influenza bacilli were separated from the broth culture by centrifugation,\* and then suspended in sodium chlorid solution. At first 50 per cent of the hemolytic streptococci were added in the form of the killed broth culture and the other 50 per cent in sodium chlorid solution suspension after centrifugation. But owing to rather severe reactions, only 25 per cent of the hemolytic streptococci are added in the form of the broth culture. The streptococci in the broth culture are killed by the addition of 0.5 per cent cresol. The centrifugated bacteria are suspended in sodium chlorid solution so that 1 c.c. represents approximately the growth from 50 c.c. of the broth culture, and are killed by the addition of 1 to 1.5 per cent purified cresol. The dense suspensions are diluted with an equal volume of sodium chlorid solution after the cultures, made twenty-four hours after the cresol is added, have remained sterile for forty-eight hours. In some instances the suspensions became slightly contaminated with *Bacillus subtilis*, when heating to 60 C. for one hour was necessary to render them completely sterile. If this was not sufficient, the suspensions were discarded. At first, owing to the urgent demand for the vaccine, the use of extreme heat in the sterilization of the broth, negative aërobic and anaërobic cultures at the end of from forty-eight to seventy-two hours were considered sufficient as sterility tests. It is now the rule to hold the vaccine until all cultures and animal tests have proved negative for one week. Blood-agar and glucose broth and glucose brain broth and litmus milk in tall columns are the mediums used for the sterility tests. It was the rule to inject a number of persons with each batch of vaccine

\* In connection with some work on poliomyelitis in which it became necessary to procure large quantities of the streptococcus, the ordinary large cup centrifuge proved inadequate. A number of centrifugal machines were tested to see if they might not facilitate greatly the clarification of broth in its preparation and to separate efficiently the bacteria from large quantities of liquid cultures. A number were found useful; but owing to the simplicity of construction and the ease with which bacteria may be obtained from the revolving bowl without contamination, the one manufactured by the Sharpless Separator Co., West Chester, Pa., was selected and has proved satisfactory for the purpose. By the use of the small laboratory size, it is possible, for example, to separate the bacteria from 50 liters of broth an hour. The revolving bowl and other utensils with which the broth comes in contact are autoclaved. A galvanized iron hood built over the machine makes it possible to sterilize the air in the hood with steam; and by siphoning the broth cultures from the bottles large quantities of bacteria may be collected without contamination.



lowing vaccination. At the State Hospital for the Insane at Rochester, with a total population of about 1500, where one case of influenza had occurred before the inoculations were given, only three cases occurred following the date of the first inoculation for a period of six weeks. With the second wave of the epidemic, however, there was a mild outbreak of the disease. This would indicate that the immunity is of short duration.

Nearly all the patients with influenza and pneumonia admitted for treatment in the hospitals in Rochester, where approximately one-half of the population has been vaccinated, have been from the uninoculated group, excluding those patients who contracted the disease elsewhere.

In one hospital in which the nurses had been inoculated no cases developed after the inoculations, although the nurses continued to care for patients with influenza. Owing to the scarcity of vaccine, some of the nurses, living under identical conditions, were not inoculated, and a high percentage of these contracted severe attacks.

Numerous instances have been observed in which protection appeared to be afforded to inoculated members of families of which all the uninoculated became ill. Similar results were obtained when conditions among the inoculated and uninoculated were comparable, such as in offices, factories, and schools, where nearly all were inoculated, or where only a small percentage were inoculated. Illustrating results are as follows:

Of 1000 persons employed by one company, 481, about one-half, received one inoculation; 224 received two inoculations, and 95 received three inoculations. From October 28th, the date of the first inoculation, to December 8th, 138 cases of influenza occurred, only 20 of which were among persons who had had one or more inoculations. Of these, 14 had had only one inoculation and the remaining 6 had but two inoculations. There were 13 deaths, only 2 of which followed influenza among the inoculated, and in these 2 cases only one inoculation had been given.

The mortality from bronchopneumonia in pregnant women has been especially high during the present epidemic. The vaccinations in a fairly large number of such persons appear to have afforded some protection against this complication. The bacteria included in the vaccine belong to the general group of microorganisms associated commonly with chronic infections, such as arthritis, sinusitis, and bronchitis; hence some effect should follow its injection. Striking instances of improvement in these conditions have been noted, but whether due to specific or non-specific effects, or whether the vaccine acts as an "exfoliative

stimulus," according to Larson, liberating preformed specific antibodies, remains to be determined.

From the results obtained thus far it appears possible to afford a definite degree of protection by prophylactic inoculation to persons against the more serious respiratory infections during the present epidemic of influenza. The duration of immunity is not known, but indications are that it is relatively short.

The vaccine should contain freshly isolated strains of the more important bacteria in approximately the proportions as found in the sputum and lungs in the disease, and since the relative proportions of the bacteria at hand differ so markedly in widely separated communities, judging by the reports, the formula of the vaccine should be made to conform as nearly as practicable to the respective flora of the disease in the communities in which the vaccine is to be used.

A saline vaccine was used as an emergency measure. Owing to the large number of different bacteria that need to be included and the large doses necessary, a lipovaccine, judging by the recent work of Whitmore, ought to possess definite advantages, since reactions should be less severe, the formation of antibodies more marked, and the resulting immunity more enduring.

TABLE 2.—INCIDENCE OF ILLNESS AND MORTALITY FOR 1000 PERSONS

	INOCULATED					UNINOCULATED
	After first inoculation	After second inoculation	Within seven days after third inoculation	Within six weeks after third inoculation	Total	
Influenza.....	23.00	10.00	9.00	14.60	56.60	229.0
Pneumonia.....	1.80	1.00	1.00	1.80	5.60	15.7
Meningitis.....	0	0	0	0	0	0.4
Encephalitis.....	0.04	0	0.05	0	0.09	0.2
Deaths from influenza or pneumonia.....	0.63	0.08	0	0.19	0.90	3.4
Total number of inoculated and uninoculated persons.....	28,459	26,150	20,792	20,792	..	61,753

I am constantly being asked with regard to the use of the vaccine in treatment. Since the severer complications in influenza, such as pneumonia, do not usually begin until the fourth day or later, the vaccine, if

stein. The tube, a small, soft-rubber catheter attached to a glass funnel, was passed by mouth and inserted about 15 cm. No injury to the babies ever resulted. The tube feeding was continued until the babies were able to nurse or take the bottle successfully. The smaller babies, weighing 2000 gm. and less, accomplished this, on the average, at the end of the first month. Only one required two months before being able to take the breast. Two-thirds of the infants with a birth weight of more than 2000 gm. took the breast successfully in the first week. Only three needed to be tube-fed in the third week.

Table 1 shows the birth weights of the babies who survived and the day on which they began to take considerable nourishment directly from the breast. Nearly half these babies, however, required complemental feedings for a week or two longer, that is, they were weighed before and after nursing, and the deficiency was made up by tube or bottle. The breast supply of the mothers was kept up by manual expression or pumping, many of them sending their milk in twice a day by messenger.

Feeding, as a rule, was begun on the second day, the initial amounts being usually from 15 to 30 gm. six times in twenty-four hours. Oberwarth, Birk and Ladd have found the daily caloric need of the premature infant to be slightly in excess of 100 calories per kilogram. Salge and Budin place the amount about 50 per cent higher, while Czerny and Keller give figures that lie between the two. According to Birk, after the tenth day, the premature baby needs about one-seventh of his body weight in breast milk daily. It would seem—and this was our experience—that no average applies to the individual baby. The chief factor to be considered is that the baby's tolerance for food must not be overstepped. Vomiting (other than an occasional slight regurgitation when the tube is withdrawn) seems to be the first danger-signal, and on numerous occasions the baby's ration was temporarily reduced when this appeared. Certainly one should not wait for other evidences of over-feeding, such as diarrhea or irregular temperature.

#### ADJUSTMENT OF TEMPERATURE

Incubators were not used. Instead, the babies, clad in flannel hoods and capes, were kept in blanket-lined clothes-baskets containing hot-water bottles. The bed temperatures were charted along with that of the baby, and held at between 85 and 90 F. Genersich gives this as the optimal temperature for the premature infant's bed. None of our

babies that were unable to maintain a normal body temperature with a bed temperature of 90 were able to do so when the bed temperature was higher. Our charts show that when the baby can maintain a normal monothermia with the aid of hot-water bottles, the temperature will remain between 98 and 99 F. without them.

TABLE 1.—BIRTH WEIGHT, CONTROL OF TEMPERATURE, AND DATE OF FIRST SUCCESSFUL NURSING IN SURVIVING INFANTS

CASE NUMBER	BIRTH WEIGHT, GM.	DAY ON WHICH TEMPERATURE WAS FIRST CONTROLLED	DAY OF FIRST SUCCESSFUL NURSING
8840.....	1505	28	32
8075.....	1540	33	48
10577.....	1640	30	42
8074.....	1670	28	71
10698.....	1710	28	21
11744.....	1800	..	34
12619.....	1800	14	10
11112.....	1870	37	19
11457.....	1925	21	12
11621.....	1930	10	26
9838.....	1940	72	67
12490.....	1960	..	18
7370.....	1965	15	6
6536.....	2000	21	34
7992.....	2000	8	30
7993.....	2050	8	28
12871.....	2060	22	12
8073.....	2120	29	25
8347.....	2135	13	1
11665.....	2180	8	10
9165.....	2260	17	10
10235.....	2280	..	2
9267.....	2300	1	4
12876.....	2300	..	6
9703.....	2370	18	15
8590.....	2380	..	3
11390.....	2400	3	4
7427.....	2440	..	5
9669.....	2440	24	5
10926.....	2450	..	4
9811.....	2455	5	2
8731.....	2480	..	2
7870.....	2595	3	6
11883.....	2630	..	9
7456.....	2815	12	4
7514.....	2860	3	3

The bed temperatures were taken and charted after artificial heat was discontinued, and in babies that were controlling their body temperatures the bed temperatures were uniformly between 85 and 90 F. The temperatures of the bed of another premature baby, whose own

TABLE 4.—PROGRESS OF SURVIVING INFANTS IN WEIGHT, CONTROL OF TEMPERATURE, NURSING ABILITY, ETC.

CASE NUMBER	WEIGHT AT BIRTH, GM.	DAY ON WHICH BABE FIRST CONTROLLED TEMPERATURE	DAY OF FIRST BOTTLE FEEDING	DAY OF FIRST BREAST FEEDING	AGE AT DISCHARGE	WEIGHT AT DISCHARGE	DAY ARTIFICIAL HEAT WAS DISCONTINUED	COMPLEMENTAL FEEDINGS NECESSARY AT DISCHARGE	NURSING WELL AT DISCHARGE	GAINING SATISFACTORILY AT DISCHARGE	REMARKS
8890	1505	28	32	32	38	1870	28	..	+	+	....
8075	1540	33	52	48	55	2360	..	+	..	+	....
10577	1640	30	..	42	49	2360	31	+	..	+	....
8074	1670	28	..	71	141	4150	74	+	+	+	....
10698	1710	28	..	21	28	1860	..	..	+	+	....
11744	1800	..	31	34	59	1910	..	..	..	..	Much artificial feeding; mother did not cooperate
12619	1800	14	4	10	59	2800	15	..	+	+	....
11112	1870	37	18	19	38	2100	16	..	+	+	....
11457	1925	21	..	12	28	2640	..	+	..	+	....
11621	1930	10	10	26	59	1830	27	..	+	+	....
9838	1940	72	67	..	168	3770	..	..	+	+	Pseudorickets
12490	1960	..	18	18	32	2120	..	..	+	..	Temperature not controlled; weight gain slight
7570	1965	15	..	6	19	1950	..	+	..	+	....
6536	2000	21	34	..	151	4350	..	..	..	+	Pseudorickets
7992	2000	8	29	30	39	2280	..	+	..	+	....
7993	2050	8	29	28	38	2380	..	+	..	+	....
12871	2060	22	..	12	31	2460	..	+	..	+	....
8073	2120	29	25	25	38	2540	..	+	..	+	....
8247	2135	13	..	1	24	2050	..	+	+	+	....
11665	2180	8	..	10	13	2520	..	+	..	+	....
9165	2260	17	..	10	25	2220	..	+	..	+	....
10235	2280	..	..	2	15	2210	..	..	+	+	....
9267	2300	1	..	4	11	2060	..	..	+	..	Temperature slightly subnormal; weight stationary
12876	2300	..	..	6	10	2290	..	+	+	+	....
9703	2370	18	..	15	26	2630	18	..	+	+	....

8590	2880			3	10	2220			Temperature not controlled; weight stationary	Temperature 97 to 98 F.	Temperature above 97 F.
11390	2400	3	11	4	11	2310	:	+	.....	.....	.....
7427	2440		5	5	11	2160	:	+	.....	.....	.....
9619	2440	24	83	5	83	2630	:	+	.....	.....	.....
10926	2450		12	4	12	2430	:	+	.....	.....	.....
9811	2455	5	10	2	10	2430	:	+	.....	.....	.....
8731	2480		12	2	12	2470	:	+	.....	.....	.....
7870	2595	3	10	6	10	2330	:	+	.....	.....	.....
11883	2630		11	9	11	2580	:	+	.....	.....	.....
7456	2815	12	16	4	16	2600	:	+	.....	.....	.....
7514	2860	3	9	3	9	2630	:	+	.....	.....	.....

when the baby is born outside the hospital. Consequently, while our mortality rate is much increased by the fourteen infants who were born there and died on the first day, it suffered very little from the deaths of infants who were brought in from outside to die later. Only one such death occurred.

Table 2 shows the birth weight, the age at death and its cause in the six infants who survived longer than five days. Similar data concerning the eighteen infants who died in the first five days are contained in Table 3. It is a question as to how many of these babies were viable.

#### PROGRESS OF SURVIVING INFANTS

A summary of the more important information gleaned from the records of the surviving babies is presented in Table 4. It shows the progress of each baby, the ability to control temperature, to nurse, and to gain in weight. The age figures are given in days, the weights in grams. The + signs in the ninth column signify that complemental feeding was still necessary at the time of discharge, those in the tenth that the baby was nursing well at discharge, and those in the eleventh that at that time he was gaining satisfactorily.

The parallelism between the ability fully to control body temperature and to gain satisfactorily in weight is noted. Six of the nine babies that were discharged before they were able to maintain a normal monothermia were not yet making a good gain. Because of the advantage of keeping the baby with its mother, all infants were discharged as soon as it seemed safe to discharge them. All but two babies, however, were either nursing well

or gaining satisfactorily at the time of leaving the hospital. Only three infants remained in the hospital longer than two months, and two of these developed marked pallor and craniotabes in the third month. As has been pointed out by Rosenstern and others, the so-called pseudorickets uniformly occurs at this period of premature life. These babies were given iron and cod-liver oil and showed improvement. It would seem advisable, if not contraindicated, to start such medication as early as the second month.

### CONCLUSION

It is found that of 60 infants fed breast milk on the four-hour interval, by tube when necessary, kept sufficiently warm and protected against infection, 36 lived and 24 died—a gross mortality of 40 per cent. When, however, one deducts the 14 deaths occurring on the first day, the mortality rate of the remaining 46 cases falls to 22 per cent.

The most favorable view of the treatment employed is gained if only the 42 babies living longer than five days are considered. Among these, including two who by better judgment and technic could have been saved, there were 6 deaths, giving a mortality of 14 per cent.

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# INTRATRACHEAL ANESTHETIC MACHINE\*

A. W. ADSON AND G. G. LITTLE

In neurologic surgery it frequently becomes necessary to employ an intratracheal anesthetic, particularly in work on the cerebellum and the brain stem, when a patient may have respiratory difficulty that may be relieved by the administration of plenty of pure air under slight pressure. There are many intratracheal anesthetic machines in use, some of which are used very successfully, but the general tendency has been to make them too complicated. In view of this fact it seemed permissible to construct a machine that would be efficient yet simple and easy to manipulate. The one herein described has been constructed to conform to three principles, as follows:

1. *Constant flow of air.*—A constant flow of air maintained and controlled so that pure air alone, or any degree of ether saturation, may be given (Fig. 409). This is accomplished by diverting the air current through valve *C* from *E* to *F*. If pure air is desired, the valve is thrown open to send the air direct from *E* to *F* without entering the ether chamber. If ether is desired, part of the air current is forced through tube *N* on the ether surface, where it becomes saturated with ether and escapes through tube *B* to tubes *C* and *F*.

2. *Ether tension.*—Ether tension is kept constant by the lowering or raising of tubes *B* and *N*.

3. *Constant air pressure.*—A safety valve prevents too great pressure within the lungs. This is accomplished by connecting the air current with a mercury manometer, *L*, *G*, and *H*.

## THE APPARATUS

The apparatus consists of a motor directly connected to a small rotary blower mounted on a suitable base; a coil of flexible metal tubing to convey the air to the controlling valve, and a three-point foot-piece with a column supporting a base plate, to which is secured a 24-ounce glass bottle by means of a yoke-clamp gripping the two side rods that

\* Reprinted from Jour. Am. Med. Assn., 1918, lxx, 1746-1747.



tube *B* into port *A* at *D*, thence to *A* and out through tube *F* and to the patient. Port *B* is extended toward *A* at *E*, leaving a thin wall between, so that as the valve is turned from "All Air" to "All Ether" there will be a constant flow of air.

To use this apparatus, the motor and blower should be placed in some cool, easily accessible place where a supply of pure air can be drawn into the pump. The starting and stopping switch should be within reach of the operating room, as should also the air pipe line from the pump. The air connection leading into the room should be about six inches above the floor, so that the flexible metal tube used to connect the con-

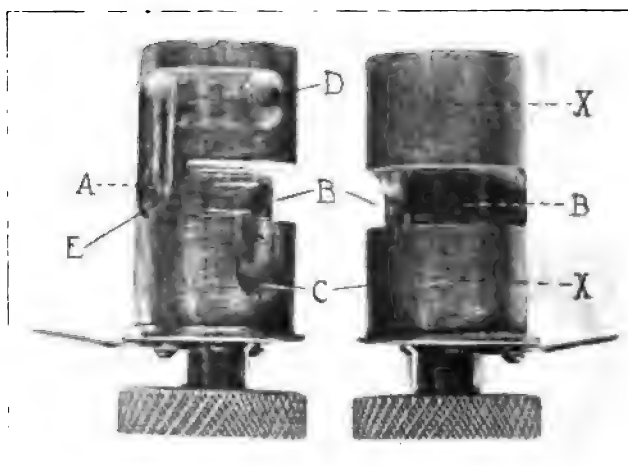


Fig. 410.—Valve.

trolling valve with the pump may lie on the floor out of the way. When the anesthetic is to be started, the rubber connection of the flexible air line is secured to tube *E*, and the intratracheal tubing to tube *F*. Valve *C* is adjusted to control the amount of ether desired. The mercury column is raised to 10 mm. for adults and 7 mm. for children. The bottle is filled with ether to 0, and tube *N* is adjusted to a level 2 cm. above the ether.

The patient to be anesthetized is given morphin and atropin one hour previously. Before intubation is attempted it is important to have the patient deeply anesthetized, after which the intratracheal catheter is inserted and connected with the running machine. Air is used first, then, gradually, the ether.

## MEDIAN BAR EXCISOR\*

W. F. BRAASCH

It is generally recognized that urinary obstruction at the vesical orifice may be caused by various conditions other than prostatic hypertrophy. Such conditions may be divided into three groups, namely, contracture of the bladder neck, glandular and inflammatory tissue formation, and congenital obstructions.

Methods have been devised for removing the obstruction caused by contraction at the vesical orifice, such as the Chetwood and modified Bottini operations and the Goldschmit technic. However, no method short of resection had been definitely suggested for the removal of obstructing glandular and inflammatory tissue until that described by Young in 1912. He demonstrated that such obstructions could be removed by endoscopic methods under local anesthesia, and without incapacitating the patient for more than a few days. The instrument he used was called a median bar excisor, and while the instrument was indeed a very serviceable one, the operator was handicapped by the fact that it did not permit of accurate inspection of the field of operation. As a result, the instrumentation could not be accomplished under the guidance of the eye.

It is a well-known fact that it is impossible to obtain a satisfactory view of the prostatic urethra without the distention of the urethra, which may be accomplished by either air or water. Air dilatation has proved unsatisfactory, so that water is the preferred medium. The median bar excisor I have been using for several years permits of clear inspection of the prostatic urethra with water distention. The instrument consists of three separate sheaths of decreasing caliber which are so arranged that the smaller sheath fits into the next larger. The outside sheath (*A*) is practically a urethroscope. The light is situated at the distal end in the beak, and it has an irrigating cock near the proximal end. The window is of plain glass without magnification and fits all

\* Reprinted from *Jour. Am. Med. Assn.*, 1918, lxx, 758, 759.

mental cause of death in each instance is a failure of physiologic compensation. From the therapeutic standpoint one of the most important problems to solve in connection with shock is to determine why some persons fail to compensate for the various procedures to which they are submitted.

I have discussed in a previous paper<sup>7</sup> the effect of the anesthetic in relation to shock, but the anesthetic is of so much importance, both in experimental and in postoperative shock, that its effect should be emphasized. Recently, while performing some experiments, I found that a low blood-pressure was produced invariably within an hour or two after the beginning of anesthesia, regardless of the experimental procedures employed. These results were proved to be due to impure ether. Careful experiments in anesthetic control should always be performed before it is concluded that an experimental procedure produces the symptoms of shock.

#### THE RELATION OF THE NERVOUS SYSTEM TO SHOCK

The relation of the nervous system, as a primary agent, to the condition which the surgeon diagnoses as shock is not clear. It is quite probable that the nervous system is a primary etiologic factor in some cases, particularly in those in which an anesthetic has not been employed. There are no experimental data extant in which such a relationship has been proved beyond a doubt. The results of numerous experiments that I have performed under light ether anesthesia have been, with the few exceptions previously recorded, uniformly negative. It certainly is possible to stimulate, either electrically or mechanically, one or all of the major nerves going to the limbs, for example, the sciatic and brachial plexus of a dog under constant surgical ether anesthesia, for as long as four hours, without producing the condition of shock. It should be emphasized that the marked fluctuation in respiration and blood-pressure that occurs following such stimulation is not shock, and shock can be said to have occurred only when the cardinal signs of the condition are present at the end of the period of stimulation. In my experiments this has not occurred, but both respiration and blood-pressure have quickly returned to approximately the normal condition. The same phenomenon follows section of the major nerves. Whether or not much reaction follows such a procedure depends mainly on the depth of the anesthesia. Under light anesthesia, section of the sciatic nerves and the brachial plexus produces marked changes in respiration and blood-pressure; when

deep anesthesia is employed, section of these nerves may produce only the slightest response in respiration or blood-pressure. In either case shock does not follow section of the nerves. We have observed animals which, under light anesthesia, have had a normal blood-pressure eight hours after section of the major nerves to each limb (Fig. 412). I am inclined to believe that, in most instances in which the primary factor is the nervous system, the cause will be found to be of the nature of inhibition, as held by Meltzer.

Under only two conditions have I been able to produce death by nerve stimulation. One condition was produced by stimulating the

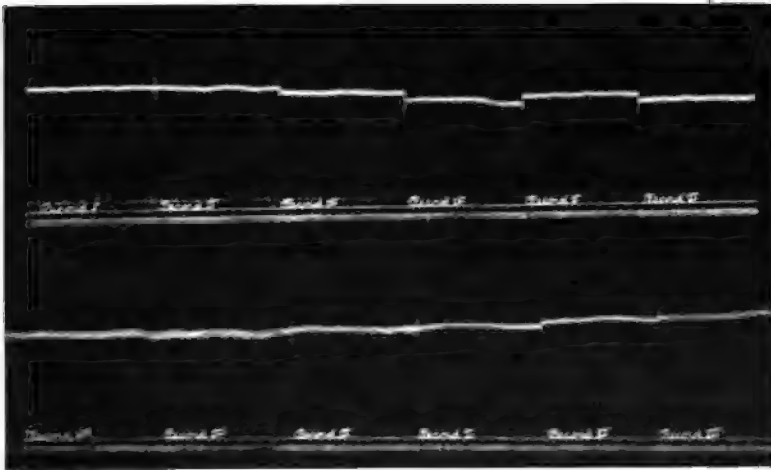


Fig. 412.—Kymograph record illustrating (1) an anesthetic control experiment and (2) the effect of section of the major nerves to each limb; Record I, normal blood-pressure (140); Record II, immediately after exposing the sciatics and brachial plexuses; Record III, immediately after section of both sciatics and brachial plexuses. Each succeeding record was taken at intervals of an hour; thus, Record XII was taken nine hours after section of the nerves, and the blood-pressure was 145.

nerve-fibers that inhibited respiration when the animal was under deep anesthesia. Ether anesthesia seems to depress, and, when the tension is great enough, abolishes all respiratory reflexes except one before respiration ceases. The reflex that it does not abolish before the respiratory center fails is the one that inhibits respiration. Instead of ether depressing this reflex, it is quite common for its action to be increased. Under deep etherization it is possible, in many instances, actually to kill the animal by prolonged stimulation of nerve-fibers that inhibit respiration. The stimulation of some nerves, as the central end of the vagus and the superior laryngeal, usually inhibits respiration for a short period.

As the stimulation is continued, however, respiratory movements soon return, owing either to a decrease in the reflex or, what is more probable, to an increase in the chemical stimulation of the nerve center. It is rarely possible, under light surgical anesthesia, to inhibit respiration by the stimulation of these nerves for a long enough period to jeopardize the life of an animal. As the ether tension is increased, the length of time the respiratory movements are inhibited is prolonged. Finally, in a large number of cases, under deep etherization, respiration fails to return, and blood-pressure quickly falls, death ensuing. In other cases, while respiration is always inhibited for a time, recovery occurs. In the earlier experiments the blood-pressure was usually decreased, as much as one-half the normal pressure, before respiration could be inhibited long enough to produce death. However, it was found that by cautiously increasing the ether tension, many animals could be killed while the blood-pressure was practically normal. The method of administering the anesthetic does not seem to be a factor in producing death. In most of our experiments the Connell apparatus was used, in some instances a modification of McGrath's method, while in still others only the cone method was used. While it is possible that death in these cases may be due to factors other than the inhibition of respiration and asphyxia, there is no evidence to show it. I have never been able to obtain this result by stimulating nerves that did not inhibit respiration. Death will not occur while insufflation or artificial respiration is maintained, if the ether tension is not above that compatible with life. Death under deep etherization has not been produced except in connection with inhibition of respiration. The process producing death in such experiments seems to be as follows:

For some unknown reason ether does not abolish reflexes that inhibit respiration as long as the respiratory center responds. Under deep etherization the threshold of the cells of the respiratory center is greatly increased to the chemical stimuli. A point is thus reached at which the center will respond to the inhibitory reflex, and not to the increased carbon dioxide in the blood. At this time the stimulation of inhibitory fibers will produce death, and, owing to the deep etherization, quite quickly in many instances. Attempts have been made to produce the same result by both methods of stimulating the nerves other than by electricity or deep etherization. To date, however, all attempts have failed (Fig. 413).

It has been thought for a long time that inhibition of the heart, due

to stimulation of the vagus, might produce death in mammals, and it has also been suggested that a reflex producing inhibition of the heart might also end fatally. In a few instances in this series of experiments such a result seems to have been produced. However, to the present time, death, owing to apparent reflex inhibition of the heart, has not been produced by stimulation of any nerve except the superior laryngeal, although it would seem that the central end of one vagus with the other



Fig. 413.—Kymograph record showing the effect of stimulating the central end of the vagus under light and deep anesthesia. Normal blood pressure was 115. At signal *a*, ether was disconnected and the control end of the left vagus was stimulated at *b* until respiratory movements returned. During the interval *D* (sixteen minutes) ether tension was increased. At *a* the ether was discontinued, and at *b* the vagus was again stimulated, and death occurred.



Fig. 414.—Kymograph record showing the effect of stimulating the superior laryngeal nerves under light anesthesia. At *a* ether was disconnected and signal *b* marks the period of stimulation of the superior laryngeal nerve, death occurring. This record is difficult to interpret, but it would appear that inhibition of the heart was the major factor producing death.

intact would be effective. As this reflex disappears under deep etherization, it appears that death could occur only by reflex inhibition of the heart under light anesthesia. Such was the case in these experiments (Fig. 414).

What practical bearing such experiments have on the shock problem cannot at present be stated. Death is produced so suddenly and so strikingly under these conditions that it seems highly probable the same thing has occurred in man. It is quite possible that deep etherization

and inhibition of respiration during the time in which operations are being performed in the region of the neck, axilla, and diaphragm (regions in which traumatic procedures are prone to produce stoppage of respiration) are responsible for some of the sudden deaths on the operating table that the surgeon has diagnosed as due to shock.

#### THE RELATION OF FLUID VOLUME TO SHOCK

The conception that in most of the cases which the surgeon diagnoses as shock the patients are in a pathologicophysologic state, in which the cause of the symptoms is a loss of circulatory fluid, has been adversely criticized, because of the clinical distinction that is made between hemorrhage and shock. This has been due, I believe, to a failure to consider the fundamental likenesses and differences between the two conditions.<sup>3</sup> The symptoms of this form of shock and of hemorrhage are, in the main, due to the loss of circulatory fluid. In general, after hemorrhage, the vascular system is capable of functioning, and the mechanism controlling fluid volume is able to at least partially compensate for the loss. In the condition of shock, however, not only is there a loss of circulatory fluid, but the mechanism which controls fluid volume is also, and possibly primarily, greatly impaired. That is the reason why, in the former condition, intravenous injection of salt solution is of distinct value, when even the so-called colloidal solutions do not remain long in the circulation in the latter condition.

Janeway and Jackson have shown that a circulatory failure, which presents the typical signs of shock, may be produced in dogs by a partial occlusion of the inferior vena cava at its point of entrance into the thorax. This has been corroborated by other investigators.<sup>4</sup> It seems that, for the most part, the result is due to the effect of the occlusion on the portal circulation and the liver, because it is well known that ligation of the inferior cava at a point just below the entrance of the hepatic veins is a perfectly safe surgical procedure in most dogs. The collateral venous return is such that a ligature thus applied does not produce any of the symptoms of shock. The ligation of the portal vein will always cause death in a few hours. Even partial occlusion of this vein, as sometimes occurs in a badly made Eck fistula, will produce death in a couple of days.

In a recent series of experiments I have attempted to determine the relation of the volume of capillary and venous beds to the signs of shock. Only a brief preliminary report can be made of these experiments.

The method consisted in including in a strong ligature all the structures to each limb except the major artery. In this manner the major artery was allowed to pump blood into the limb, from which all venous and lymph return was obstructed. The results of a sufficiently large series of experiments are in general agreement. The first effect of such a procedure is a slight and ordinarily transient rise in blood-pressure. The blood-pressure, as a rule, soon decreases and at the end of two hours it has only about half its initial value. At this time the animal generally exhibits the signs of shock. If the ligatures are then removed, recovery usually takes place. When the ligatures are left on for a long period of time, there may be an initial rise in pressure following their removal, but it subsequently decreases. When the ligatures have been applied for a very long period, the removal produces a further drop in blood-pressure, and eventually, death. To a lesser degree these results may be obtained when only three limbs are used. From the results of such experiments it would seem that a condition producing stasis in a large capillary field would produce the signs of shock. It should be emphasized that simple vasomotor dilatation will not cause this condition. Section of the nerve supply to all the limbs does not produce the signs of shock (Fig. 412).

#### THE TREATMENT OF SHOCK

The treatment of shock may be divided into: (1) General measures; (2) the use of drugs; (3) attempts to restore the fluid volume; and (4) special measures. In studying any form of treatment of shock experimentally, it is necessary carefully to standardize the experimental procedures. In this series of investigations the routine method of experimentation was as follows:

The animal (dog) was etherized in a closed cabinet, intubated, and a constant surgical anesthesia maintained by means of the Connell apparatus. The carotid blood-pressure was recorded with a mercury manometer. Marked changes in the temperature were prevented by the judicious use of an electric pad. After a normal record had been obtained, the abdominal viscera were exposed and gently sponged, about every fifteen minutes, with dry gauze. When the blood-pressure had decreased and remained rather stationary at the desired point, which occurred usually from about one to two hours after exposure of the viscera, the viscera were returned to the abdominal cavity and the wound was repaired. After waiting a sufficient length of time to deter-



mine definitely that the blood-pressure did not increase, the procedure designated to improve the condition of the animal was instituted. The blood-pressure was taken as a criterion of the condition of the animal because it is the easiest indication to record and compare. It should be emphasized that the anesthetic was constant throughout the experiment. This removes the possibility of the ether producing an error in either the interpretation of the blood-pressure record or the general condition of the animal. Careful anesthetic control experiments were performed, the etherization being maintained at the same tension and for a length of time equal to the shock experiment. It should be noted that practical conclusions can be drawn only from the results obtained as applying to a condition in which the signs of shock were produced by exposure of the abdominal viscera. If the blood-pressure is allowed to decrease until it is much less than half the normal pressure, it is rarely possible to restore it by any known method. This is an important point to consider in placing a value on any method of treatment.

The general measures employed consisted of placing the animal in the head-down position, and the application of heat, etc. A slight amount of benefit has been obtained by such methods in experimental shock. In fact, it was found to be of distinct value to keep a heating pad under the animal throughout the experiment, care being taken to apply only a moderate amount of heat.

Drugs are employed for one or two purposes—either as a stimulant to the circulatory system, as strychnin and camphorated oil, or to produce vasomotor constriction, as epinephrin or pituitary extract. The results of the experiments corroborate our previous investigation on the use of stimulants in experimental shock. In none of the experiments was any benefit derived.

The value of the use of vasoconstrictors in the treatment of shock is still an open question. In the first place, although the decrease in blood-pressure is of great importance in shock, it is not known whether or not its increase by means of vasomotor constriction is in itself of much permanent benefit to the organism. In the second place, none of the vasomotor constrictor drugs produce a very prolonged effect. In experimental shock it is not possible to maintain blood-pressure for a very long period of time near to the normal value by the use of the vasoconstrictor drugs. In our experience pituitary extract produced a more prolonged action, and seemed to be of somewhat greater benefit than epinephrin.

A large number of artificial fluids have been devised with which to attempt to restore the volume of fluid in shock. Our series does not yet include experiments from which positive conclusions may be drawn in regard to all of these. However, they have furnished enough data to justify some tentative conclusions in regard to their use in experimental shock.

1. Physiologic sodium chlorid solution is the least valuable of all the artificial fluids, although hypertonic sodium chlorid solutions are of value.

2. The making of the artificial fluid alkaline definitely enhances its value.

3. The use of glucose in the injected solution is also of definite value.

4. None of the saline solutions alone will maintain blood-pressure for more than a very short period of time, even when it has been lowered to but a slight degree by exposure of the abdominal viscera.

5. The employment of the so-called colloidal solutions, such as those containing acacia or gelatin, is of distinct value. The intravenous injection of these fluids will often restore and maintain the blood-pressure for several hours after it has been decreased to at least one-half its normal value by the exposure of the abdominal viscera.

6. From these results it would seem that the ideal artificial fluid should contain—(a) some substance to increase its colloidal properties; (b) an alkaline salt, and (c) glucose.

7. It should be noted that none of the artificial fluids will give as good results as whole blood or blood-serum.

The value of transfusion in the treatment of shock is well known. In this series of experiments citrated blood produced very good results. In order, however, approximately to restore blood-pressure and maintain it, the amount transfused must be comparatively large. About 30 c.c. per kilogram produced the best experimental results. Such an injection will restore and maintain blood-pressure under the experimental conditions outlined herein.

Blood serum seems never to have been used in the treatment of shock. In our experiments the intravenous injection of homologous serum has produced good results, and, in most experiments, better results, than any of the methods employed in the treatment of experimental shock. In none of the experiments in which the blood-pressure had not decreased below one-half of its original volume did the injection of serum fail to

# STUDIES ON EXPERIMENTAL SURGICAL SHOCK\*

F. C. MANN

## I. GENERAL CONSIDERATIONS OF EXPERIMENTAL SURGICAL SHOCK

In the consideration of the entire field of surgical shock from the experimental point of view, two features must be emphasized: (a) That the condition termed shock by the surgeon is undoubtedly owing to a large number of causes; and (b) that experimentally it is very difficult to reproduce the environment and all the phenomena which the surgeon calls shock.

The present series of studies has been made in order to give experimental data of as many conditions as possible which the surgeon might diagnose as shock. The data are based on a very large number of experiments performed since the first studies were undertaken, in 1912, up to the present time. For purposes of investigation I have found it of practical value to classify the various conditions into two groups. In the first group are those cases in which the cardinal signs of the condition, such as decreased consciousness, decreased blood-pressure, shallow, gasping respiration, subnormal temperature, etc., develop and supervene for some time after the exciting cause. In the second group are those cases in which a severe or fatal issue follows immediately or very closely on the action of the exciting agent.

Clinically, the first group would include most of the cases which the present-day surgeon diagnoses as shock; the chief of these would be the shock following operation. A condition presenting the clinical signs of shock and which is supposed to present a physiologico-pathologic condition similar to that in the cases in the first group, may be produced by a variety of methods. The most important of these are deep anesthesia, hemorrhage, exposure of the abdominal viscera, the use of excessive heat or cold, the isolation of large vascular areas as the partial occlusion of the vena cava, the production of cerebral anemia and the injection of drugs, peptones, and oils.

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It may be seen from the foregoing that but few of the methods used to produce the shock condition can be compared to the manner in which shock occurs clinically. Most of the methods aim, primarily, at a reduction of blood pressure. It is definitely known that some of them, and probably most of them, produce a decrease in the volume of circulating fluid. While the studies following these various methods of producing an experimental condition having the signs of shock have been of inestimable value in that they have added to the knowledge of the physiology of low blood-pressure, it should be noted that they explain in only a limited number of cases what the possible etiologic factors in shock could be.

The second group, clinically, includes most of the classical cases of shock given in the literature of the subject. It was in reference to this type of case that the term shock was first applied, namely, when sudden death occurs or alarming symptoms develop immediately following an accident or operative procedure in which no definite cause of death is found. It is shock of this type, particularly that occurring in the operating room, that has strongly impressed the surgeon with the idea that the nervous system is essentially and primarily at fault in the production of shock.

The environment reproducing the condition included in the second group is hard to obtain experimentally. Very little experimental work has therefore been done on the investigation of sudden death associated with accidental trauma or trauma occurring in the operating room. The crushing of joints in decerebrated animals has occasionally produced death, and the sudden trauma to the whole thigh of an anesthetized animal has also been fatal.\* In general, experimental work has not reduplicated the clinical observations in regard to the class of cases included in this group.

Practically all investigators of the shock problem have undertaken the investigation with the idea of proving or disproving some particular theory regarding it. Since the condition termed shock is probably due to a large number of factors, our researches must necessarily have to do with the many possible causes of obscure death. As further data are presented it seems that each of the theories developed to explain the condition of shock contains an element of truth, and that typical cases diagnosed as shock could be found to illustrate each theory. In the present studies no attempt has been made to correlate the data with

\* Personal communication from Dr. E. D. Brown.

any of the current theories, but all experiments have been devised with the view to determine some facts in regard to the many phases of the shock problem.

I am fully aware that all of these studies are not directly associated with the shock problem. However, until a comprehensive and scientific definition of shock based on known facts is made, it seems best to classify all data bearing on the causes of sudden death, the causes of low blood-pressure and the phenomena of shock under the general term surgical shock. A fact that is universally true of experimental work and especially true in regard to shock should also be emphasized, namely, that direct clinical application of the experimental data should be cautiously made.

## II. ETHER ANESTHESIA IN RELATION TO SURGICAL SHOCK

The anesthetic is of the greatest importance to the clinician in a consideration of post-operative shock. It is of even greater importance to the experimental investigator who would attempt to determine the causative factors in this consideration.

All our experiments have been performed under ether anesthesia and, therefore, all conclusions drawn must be in regard to that anesthetic only. There were two reasons for the use of ether. First, it is the anesthetic used in the greater number of operations and, therefore, the results obtained will have the greatest clinical application; second, it is the anesthetic which can be most easily employed in experimental work.

In the beginning of our work on the relation of ether anesthesia to shock, we attempted to establish some definite data in regard to the activity of the various organs, nerve centers and reflexes under different tensions of ether. Boothby, by means of the Connell anesthesiometer, showed that in man the anesthesia became complete at a definite tension of ether. It is reasonable to suppose that animals would react to ether in a like manner and that a standardization of ether anesthesia in reference to physiologic research would be accomplished. Two great difficulties were, however, encountered. First, the Connell anesthesiometers which we personally used and as tested by the Waller gas balance, were found to have too large an error for standardization, and second, the only ether to be obtained at present is not pure enough for accurate work. These two sources of error, which we have not as yet been able to obviate, have necessitated the use of approximations only in relation to ether tensions. The errors in these approximations are on an average

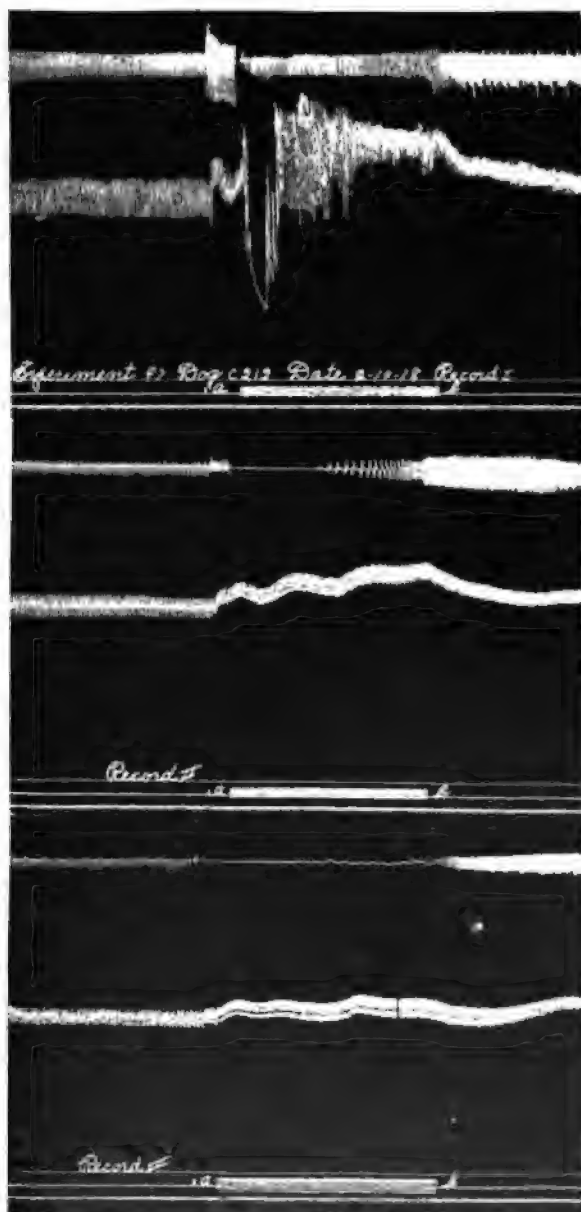


Fig. 415.—Photograph of kymograph record showing the effect of different tensions of ether on the inhibitory reflex of respiration. In each record signal *a* marks the time of disconnecting the ether and signal *b* the stimulation of the right superior laryngeal nerve for two minutes. Both vagi are intact. In Record 1 ether tension was 40 (uncorrected) and blood-pressure was 150. Note that there was but slight inhibition of respiration. The heart was inhibited. Ether tension was gradually increased and in record 2 blood-pressure was still 150 but respiration was decreased in rate and amplitude. Note the increase in the time respiration was inhibited. Record 3 shows the effect of another increase in the tension of ether. Respiration is inhibited for a much longer period.

probably no greater than 15 per cent. However, the data have justified several conclusions that have been of great value in our work on shock. These conclusions all have reference to ether anesthesia, as administered by an anesthetometer.

1. In general, the physiologic phenomena due to ether are remarkably constant at the same range of tensions in different dogs.

2. Under a low tension of ether, just sufficient to produce narcosis, the blood-pressure remains normal for a period of at least twelve hours.

3. The various respiratory and vascular reflexes disappear at different ranges of ether tension.

4. The signs of shock can be readily produced by high tensions of ether.

It is possible for practical purposes to divide ether tensions in relation to their anesthetic action into four groups. In the first group are included the tensions that are too low to produce anesthesia. The second group includes those under which the animal is reduced to a state of surgical anesthesia, but which are not high enough to depress any of the vital processes; it is impossible to kill an animal by any tension in this group, if time is not allowed to become a factor. The third group includes the tensions that produce depression of the vital processes and under which death may occur. Any tension higher than those included in this third group is incompatible with life. The range of tensions included in these various groups is approximately constant for the various animals. Of course, individual variations occur but these are usually within the limit of the error of the mechanism.

The employment of approximate ether tensions has been productive of several important findings. By the use of low tensions it can be demonstrated that an animal may be maintained in as normal a condition as it is possible to keep a narcotized animal, for many hours. This is of great value since it is thus possible to maintain a safe degree of anesthesia without its being affected by any physiologic condition of the animal or by operative procedures. It is also of great value, especially in shock experiments, to be able to administer a tension of ether which is definitely known to be too low to maintain surgical anesthesia. It is thus possible, without completely withdrawing the ether, to know when the animal has reached shock.

The respiratory and vascular reflexes undoubtedly vary under different tensions of ether but are fairly constant under the same tensions. Some reflexes are very sensitive to ether and cannot be elicited except

under low tension. Other reflexes will persist as long as the involved nerve cells functionate. In the study of any particular reflex it is of as much importance to keep the anesthetic constant as to keep the strength and rate of stimulus constant. This is impossible under most of the methods of anesthesia.

A review of protocols dealing with studies of experimental shock shows that in many instances the investigator was undoubtedly studying

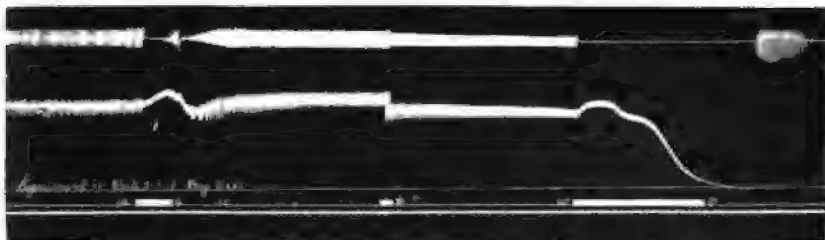


Fig. 416.—Kymograph record of respiration and blood-pressure. The animal at first was under a moderate ether tension (42 uncorrected). The right vagus was sectioned; the left vagus was intact. At signal *A* ether was disconnected and at signal *B* the central end of the right vagus was stimulated until respiratory movements, which were inhibited at first, returned. This occupied forty seconds. At signal *C* ether was again administered. Signal *D* marks an interval of fifteen minutes during which a high ether tension was administered (64 uncorrected). At signal *A'* ether was again disconnected and at *B'* the central end of the right vagus was stimulated for three minutes. Respiration was inhibited and after an initial rise blood-pressure fell to zero.

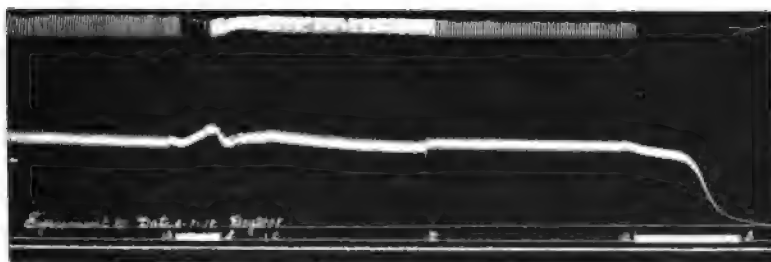


Fig. 417.—Photograph of kymograph record of respiration and blood-pressure. The procedure and results in this experiment were almost identical with those shown in Figure 416. The minor differences are: the initial blood-pressure was 120 and the uncorrected ether tension was 40; signal *D* represents a period of fourteen minutes.

a condition of deep etherization and not of shock. This is probably one of the most important reasons why so much of the experimental data on shock is contradictory. The relation of deep etherization to the signs of shock cannot be too strongly emphasized. By the manipulations of the various tensions of ether it is possible to parallel the various stages and signs of shock. Under high tensions the blood-pressure is decreased and all the other symptoms follow. However, it is quite possible to saturate an animal with ether at a tension just slightly lower than that



necessary to abolish the eye reflex and to produce an obtundity of the reflexes without decreasing the blood-pressure to a shock level. It is possible to obtain such results with a certainty only when the ether is administered mechanically and is not dependent in any way on the respiratory efforts of the animal.

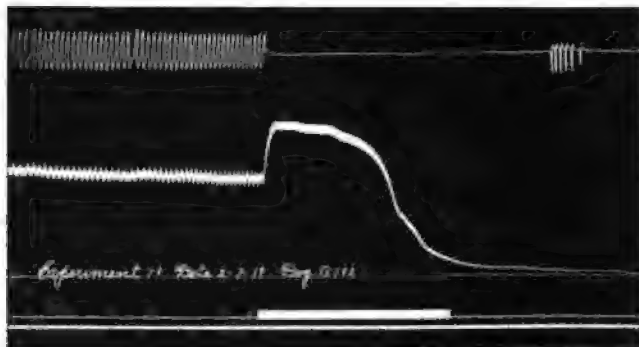


Fig. 418.—Kymograph record of blood-pressure and respiration. The animal was under a tension of ether which just abolished the eye reflex. Respiration was fifteen per minute and blood-pressure was 105. Both vagi were sectioned. Ether was disconnected just previous to the period of stimulation. The central end of the left vagus was stimulated for two minutes and forty-five seconds. Death followed and was associated with inhibition of respiration and an initial rise in blood-pressure.

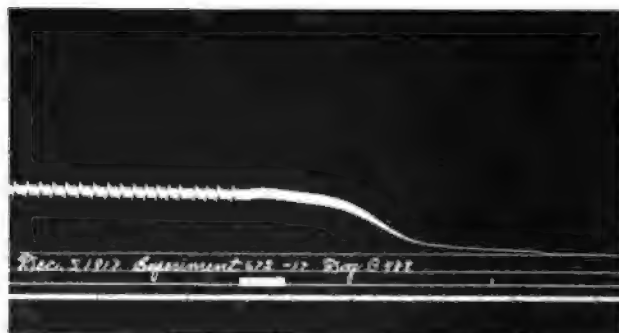


Fig. 419.—Photograph of kymograph record showing sudden death following stimulation of the central end of the right vagus for thirty seconds under a high ether tension. Both vagi were sectioned. The animal had been under ether for several hours and under the same tension (58 uncorrected) for one hour. The blood-pressure and respiration had been practically constant for the half hour preceding the stimulation. This record proves that death was certainly associated with an active inhibition of respiration.

### III. REFLEX INHIBITION OF RESPIRATION AS A CAUSE OF SUDDEN DEATH DURING OPERATION

In a study of the vascular and respiratory reflexes under various tensions of ether<sup>7, 8</sup> it was found that all the respiratory reflexes, except that which produces inhibition of respiratory movements, disappeared

before the respiratory center failed. The excitatory respiratory reflexes disappear under a relatively high tension of ether. On the contrary, instead of a depression of the inhibitory reflex being caused by ether, a relative increase at least is quite common. Thus it was possible under deep etherization, in some instances, actually to kill an animal by prolonged stimulation of the nerve fibers that inhibit respiration. It was believed that this phenomenon might have some bearing on the shock problem; a more complete study of it was therefore made.

The idea that death could actually be produced by the action of a nerve reflex has been very prevalent with clinicians, but has very little clinical or experimental evidence to support it. For this reason our experiments are important even if all the factors involved have not been determined, and even if it is not possible at the present time to make a definite clinical application of the data.

The experiments were performed on dogs. The animals were etherized in a closed cabinet, intubated and the anesthesia usually maintained with a Connell anesthesiometer. In some experiments a modified McGrath method of anesthesia was employed in order to determine if the method of administering ether were a factor in the results obtained. Respiration and carotid blood-pressure were recorded (mercury, and in some experiments, membrane manometer). Ether was always discontinued during the periods of stimulation. The nerves were stimulated electrically in the usual manner, care being taken to keep the stimulus as near constant as possible for each experiment. In many experiments shield electrodes were used. The stimulus was always maximum in strength and rate.

From the results of the stimulation of the nerves in a large series of animals it was found that only two that were easily exposed could be relied on consistently to produce reflex inhibition of respiration. Stimulation of other nerves, such as the brachial plexus, occasionally caused

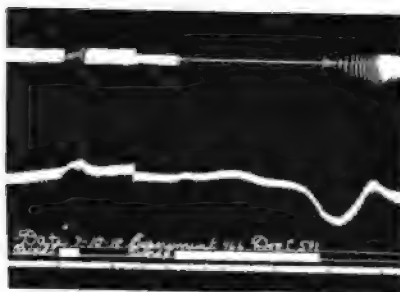


Fig. 420.—Photograph of kymograph record showing recovery after a long period of inhibition. McGrath's method of anesthesia was used. The right vagus was sectioned, the left vagus was intact. Stimulation of the central end of right vagus under light ether produced partial inhibition of respiration for less than fifteen seconds (Record 1). The ether tension was then increased until the eye reflex had just disappeared. Stimulation of the central end of the right vagus now inhibited respiration completely for the entire period of stimulation. When death appeared inevitable stimulation was stopped. Respiratory movements immediately occurred and the animal soon recovered (Record 2). This record proves that at least in some instances death following inhibition of respiration under deep ether is an active process throughout.

a cessation of respiratory movements, but only the superior laryngeal and the central ends of the vagi produced constant results. Without doubt, however, the same results may be obtained by the stimulation of other nerves when they are found to inhibit respiration, particularly those nerves containing sensory fibers supplying the upper respiratory tract.

The stimulation of either the superior laryngeal or the central end of a vagus nerve under light surgical anesthesia usually inhibits respira-



Fig. 421.—Photograph of kymograph record showing increase in the inhibitory reflex of respiration under high ether tension. Both vagi were sectioned. In Record 6 blood-pressure was 120 and ether tension 30 (uncorrected). Stimulation of the central end of the right vagus for one minute produced inhibition of respiration for about half that period. The ether tension was then increased to 70 (uncorrected). When the eye reflex had just disappeared the vagus was again stimulated (Record 7). Blood-pressure had decreased to 90. The stimulation was maintained for two minutes and respiration was completely inhibited. It remained inhibited after the cessation of stimulation and blood-pressure continued to fall. Insufflation was then started and in a short time recovery took place. This record shows that lack of air appears to be the important factor.

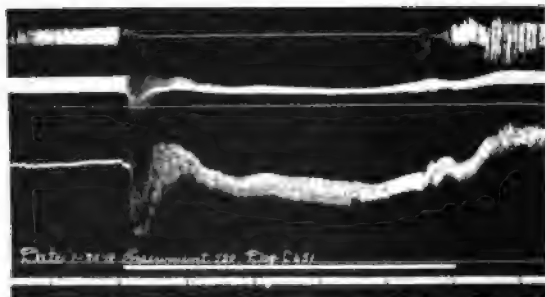


Fig. 422.—Photograph of kymograph record showing a long period of inhibition of respiration associated with reflex inhibition of the heart following stimulation of the right superior laryngeal nerve under very low ether tension. The right vagus was sectioned, the left vagus was intact. Under a high ether tension such a long period of inhibition would probably have proved fatal owing to failure of the circulation. This record shows that, while under very light ether tension it is rarely possible to inhibit respiration for a long period of time, a fatal result does not occur.

tion for a short period. As the stimulation is continued, however, respiratory movements soon return, due either to a decrease in the reflex or, what is more probable, to an increase in the chemical stimulation of the center. It is rarely possible, under light surgical anesthesia, to inhibit respiration by the stimulation of these nerves for a long enough

period to jeopardize the life of the animal. In our experiments, excluding those in which reflex inhibition of the heart was associated with the inhibition of respiration, blood-pressure was never permanently lowered to a shock pressure. In a few experiments, however, there was marked depression of the blood-pressure owing probably to stimulation of the depressor nerve, and complete recovery did not take place. Under ether tensions considerably less than those necessary to produce surgical narcosis, reflex inhibition of respiration might become dangerous provided the circulation was not capable of compensating for a long period of asphyxia. As the ether tension is increased the length of time that the respiratory movements are inhibited by the stimulation of those nerves is prolonged. Finally, in a large number of animals under deep etherization, the respiration fails to return; the blood-pressure quickly falls and death ensues. Quite frequently death can be produced by reflex inhibition of respiration under an ether tension which will just abolish the eye reflex. A fatal result did not always occur in our experiments but the respiration, with very few exceptions, was inhibited for a much longer time under deep etherization than under light anesthesia; the opposite was rarely true.

In the earlier experiments the normal blood-pressure was usually decreased as much as one-half before respiration could be inhibited



Fig. 429.—Photograph of kymograph record showing a typical result following ligation of all the structures in the limbs except the major artery. Animal etherized at 8:40. Method—amesthetometer. Aqueous arranged to record carotid blood-pressure, major artery to each limb exposed. Record 1 taken at 9:25, blood pressure 100. Ligatures were applied to each limb including all structures except the major artery. Record 2 taken at 9:40, blood pressure 130. Record 3 taken at 10:40, blood pressure 114. Record 4 taken at 11:40, blood pressure 80. Animal developing the signs of shock. Ligatures removed at 12:44. Record 5 taken at 12:45, blood pressure 88.

long enough to produce death. However, it was found that by cautiously increasing the ether tension many animals could be killed while the blood-pressure was practically normal. It was determined that such results are not dependent on the method of anesthesia or the height of blood-pressure, and that they are obtained with sectioned and intact vagi.

The mechanism by means of which death is produced, associated with an inhibitory reflex of respiration under deep etherization, is not clearly defined. In our experiments death occurred only when the nerves that inhibit respiration were stimulated, and it was never produced under deep etherization when respiratory movements were maintained. Death will not take place while insufflation or artificial respiration is maintained. The processes producing death seem to have been as follows:

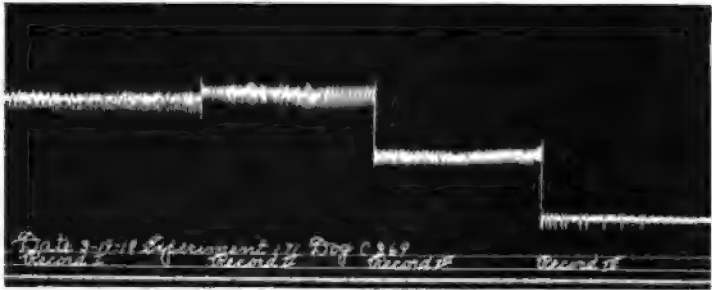


Fig. 424.—Photograph of kymograph record showing a rapidly fatal termination following venous obstruction to all the limbs. Animal etherized at 8:30; method—modified McGrath. Apparatus arranged to record carotid blood-pressure. Major artery to each limb exposed. Record 1 taken at 8:55, blood-pressure 130. Ligatures were immediately applied to each limb including all structures except the major artery. Record 2 taken at 9:00, blood-pressure 140. Record 3 taken at 10:00, blood-pressure 86. Animal beginning to exhibit signs of shock. Record 4 taken at 10:30, blood-pressure 34. The ligatures were now removed but the animal died during this procedure.

For some unknown reason, ether does not abolish the reflexes which inhibit respiration so long as the respiratory center responds. Under deep etherization the threshold of the cells of the respiratory center is greatly increased to the chemical stimuli. A point is thus reached at which the irritability of the center is so depressed by ether that it will not respond to the increasing amounts of carbon dioxide in the blood or to the excitatory reflexes, but will respond to the inhibitory reflexes. At this time stimulation of inhibitory fibers will produce death and, owing to the action of the high tension of ether on the circulation, a very short period of asphyxia will produce death very quickly. The ether tension under which death will follow the stimulation of the reflexes inhibiting respiration is fairly constant, although individual variations occur.

There seems to be factors other than deep etherization, although probably minor ones, involved in these experiments. The reflex producing inhibition of respiration seems very resistant to agencies which usually depress or abolish the excitatory reflexes of respiration. Thus it seems quite possible that most conditions which decrease the irritability of the respiratory center might allow death to occur by reflex inhibition of respiration providing the circulation were also depressed. The production of deep anesthesia, although probably the most common and potent, would be only one of these agencies.

The accumulation of the data substantiating the idea that depression of the respiratory center associated with a depressed circulation is the important factor is not complete and further investigation in regard to it is being carried on. The following suggestive facts, however, have been obtained: The inhibitory reflex of respiration is decreased or completely abolished during periods of hyperpnea; the period of apnea following hyperpnea under light ether anesthesia is not increased by the stimulation of the nerves which inhibit respiration, and the inhibitory reflex is decreased or abolished during the period of increased respiratory movements in the first stage of asphyxia. An animal cannot be killed by reflex inhibition of respiration during the first stage of asphyxia. However, as asphyxia is prolonged and the respiratory movements begin to decrease, stimulation of inhibitory nerves will inhibit respiration and in many experiments produce sudden death. In some experiments, while the time during which respiration is inhibited under deep ether is greatly increased over that under light ether, death cannot be produced. A slight period of asphyxia will increase the time of inhibition so that death will occur. It would seem that the lack of oxygen may be a



Fig. 425.—Photograph of kymograph record showing slight recovery after removal of ligatures. Animal etherized at 1:49; method—modified Sitô bath. Apparatus arranged to record carotid blood-pressure. Major artery to each limb exposed. Record 1 taken at 1:55, blood-pressure 156. Ligatures were applied to each limb including all structures except the major artery immediately after taking this record. Record 2 taken at 2:05, blood pressure 180. Record 3 taken at 3:00, blood-pressure 65. Animal exhibited signs of shock. The wire ligatures were removed at 3:04. Record 4 taken at 3:15, blood-pressure 78. Record 5 taken at 4:00, blood-pressure 50. Record 6 taken at 4:45, blood-pressure 50.

factor. Inhibition of respiration under deep etherization frequently produces death very quickly. The blood-pressure usually decreases at once and the heart soon stops beating. This result would seem to imply that death was due to or associated with other factors than

asphyxia. However, a comparison of the curves in instances in which death was due to asphyxia under deep ether shows a close similarity to those found in the condition produced experimentally. The asphyxia under deep ether seems to explain the sudden decrease in blood-pressure and stoppage of the heart, although an active process may be involved.

Under light surgical anesthesia respiration is seldom inhibited for a very long time. In a few of our experiments stimulation of the superior laryngeal nerves under an ether tension slightly too low for surgical work has produced a partial inhibition of respiration for as long as four to eight minutes. This period of inhibition is longer than that which produced death in several of the experiments under deep ether. Under the very low ether tension, however, blood-pressure remained practically normal and death did not occur. Undoubtedly, if a high ether tension had been used, death would have followed such prolonged periods of inhibition. These results would furnish some support to the idea that the sudden death following inhibition of respiration under a high ether tension was mainly owing to a failure of the organism to compensate for the asphyxiation when saturated with a high ether tension. This relation of asphyxia to deep etherization has been pre-



Fig. 424. — Photograph of record showing a sudden delayed drop in blood-pressure and partial recovery after removal of the ligatures. Animal etherized at 8:30; method — anasthetometer. The apparatus was arranged to record carotid blood-pressure. The major artery in each limb was exposed. Record 1 taken at 9:05, blood-pressure 120. Ligatures were applied to each limb, including all structures except the major artery, between 9:10 and 9:15. Record 2 taken at 9:15, blood-pressure 120. Record 3 taken at 10:15, blood-pressure 102. Record 4 taken at 11:15, blood-pressure 92. Animal beginning to exhibit signs of shock. Record 5 taken at 12:15, blood-pressure 30. Ligatures were removed immediately after taking Record 5. Record 6 taken at 12:40, blood-pressure 60.

viously discussed by Gatch, Gann, and Mann. The important fact shown in these experiments is that the inhibitory reflex of respiration under ether anesthesia persists as long as respiratory movements occur.

Experiments dealing with the attempt to produce death by stimu-

lating nerves other than electrically, and under conditions other than deep etherization, are not complete. However, it would seem quite possible to produce a condition of depression of the respiratory center by asphyxia, oxygen-lack, or other methods, without otherwise greatly disturbing the general condition of the animal, so that the stretching of a nerve or the pulling of the mesentery might produce a serious or fatal condition owing to inhibition of respiration.\*

What practical bearing such experiments have on the shock problem, it is impossible to state at the present time. Death is produced so suddenly and strikingly under these conditions that it seems highly probable the same effects have occurred in man.† It is quite possible that deep etherization and inhibition of respiration, while operations are being performed in the region of the neck, axilla, and diaphragm, regions in which traumatic procedures are prone to produce stoppage of respiration, are responsible for some of the sudden deaths on the operating table which the surgeon has diagnosed as due to shock. It should be noted that the depth of anesthesia at which inhibitory reflexes become dangerous is no greater than that which some surgeons employ.

#### SUMMARY

Ether tensions that will decrease or abolish the excitatory reflexes of respiration do not seem to depress the inhibitory reflexes, and in most instances the action of the inhibitory reflex seems to be increased, although this may be only a relative result. Ether tensions that will depress the respiratory center so that it will not respond to the increase of carbon dioxide in the blood usually will not abolish the inhibitory reflex. Under such conditions stimulation of the nerves inhibiting respiration will quite frequently produce death. This may be the process by means of which sudden death is produced during operation. However, death due to inhibition of respiration should never occur under light surgical anesthesia.

#### IV. THE RELATION OF THE CAPILLARY AND VENOUS BEDS TO THE SIGNS OF SHOCK

This investigation was made for the purpose of determining the smallest capillary and venous area which could be made to contain enough

\* In an excellent article on shock, Webster shows a kymograph tracing in which pulling on the mesentery in a shocked animal produced inhibition of respiration and death.

† Hewitt reports a case in which respiratory failure occurred during abdominal incision, but artificial respiration was effective. The corneal reflex had disappeared. Results in this case seem to parallel our experiment.



fluid to produce the signs of shock. There is no doubt that the cause of the condition which the surgeon calls shock is, in a large number of cases, a loss of circulating fluid. The method by means of which this fluid is lost to the circulation is not known nor is its place of sequestration fully established. It has been shown that the capacity of the vascular system in the splanchnic area is such that it would hold several times the normal amount of blood. There is also no doubt but that in shock due to exposure of the abdominal viscera the initial loss of fluid takes place in this area. What relation the remaining capillary and venous area of the body bears to the loss of circulating fluid is not known. Cannon believes, and has presented data to substantiate the belief, that the lost fluid is due to capillary stagnation.

Janeway and Jackson have shown that a circulatory failure which presents the typical signs of shock can be produced in dogs by a partial occlusion of the inferior vena cava at its point of entrance into the thorax. This has been corroborated by other observers.<sup>3</sup>

The method of investigation in this series of experiments consisted in including in one single strong ligature all the structures to each limb except the major artery. In this way the major artery was allowed to pump blood into the limb from which all venous and lymph return was obstructed. The animal was maintained under a constant ether anesthesia and carotid blood-pressure was recorded (mercury manometer). The ligatures were always applied so as to include as much of the limb as possible. Under such experimental conditions three results might occur: (a) Stagnation of circulatory fluid in the occluded venous and capillary areas to their full capacity.

The general effects of this loss of fluid would depend on the size of the area involved, and the ability of the remainder of the tissues to com-



Fig. 427. — Photograph of kymograph record showing slight recovery and then failure after removal of the ligatures. Animal etherized at 9:25; method—amalgamometer. The apparatus was arranged to record carotid blood-pressure. Record 1 taken at 9:45; blood-pressure 126. Ligatures were applied to each limb, including all structures except the major artery, between 9:51 to 10:00. Record 2 taken at 10:00; blood-pressure 108. Record 3 taken at 11:00; blood-pressure 76. Animal beginning to exhibit the signs of shock. Record 4 taken at 11:30; blood-pressure 45. The ligatures were removed at 11:35 to 11:40. Record 5 taken at 12:10; blood-pressure 60. Record 6 taken at 12:10; blood-pressure 50.

pensate for the loss. (b) Injury, owing to lack of proper circulation, to all the tissues of this region. (c) After removal of the ligatures, the passage into the general circulation of toxic products which might have been formed during the period of occlusion.

The results of a large series of experiments are in general agreement. The first result of ligating the limbs in the manner described is usually a slight and transient rise in blood-pressure, although occasionally the pressure may decrease from the beginning. In any event the blood-pressure soon decreases and at the end of two hours has only about one-half its initial value. Usually this decrease takes place very gradually but sometimes it drops suddenly after having been maintained at approximately its normal level for a long time. Other signs of shock also develop; for example, a short time after the application of the ligatures to the limbs it is usually possible to decrease the ether tension to a point greatly below that necessary to maintain anesthesia in a normal animal. Thus, at the end of two hours after ligation, an animal usually exhibits the major signs of shock.

If the ligatures are removed after blood-pressure has decreased about one-half of its initial value, one of two results follows: blood-pressure either increases or decreases. In the majority of our experiments blood-pressure increased after the removal of the ligatures, but complete recovery did not occur. This rise in pressure was seldom long maintained but soon decreased again, and within an hour or so was as low as when the ligatures were removed. In some of the experiments the blood-pressure fell immediately after the removal of the ligatures. In most of the animals death soon occurred, although in a few the blood-pressure was maintained at that low level for a long period of time. The

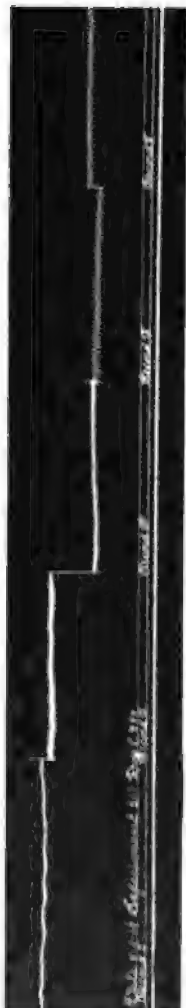


Fig. 428. Photograph of kymograph record showing partial recovery after removal of the ligatures. Animal etherized at 2:25; method—arteriometer. The apparatus was arranged to record occluded blood-pressure. The major artery to each limb was exposed. Record 1 taken at 3:04, blood-pressure 118. Ligatures were immediately applied to each limb, including all structures except the major artery. Record 2 taken at 3:15, blood-pressure 116. Record 3 taken at 3:45, blood-pressure 106. Record 4 taken at 4:45, blood-pressure 88. The signs of shock. Record 5 taken at 12:15, blood-pressure 88. Ligatures were removed immediately after taking this record.

results of the experiments may be best explained as follows: The initial fall in blood-pressure is probably due to the occlusion and stagnation of circulatory fluid in the isolated capillary and venous areas. The variation in the length of time in which the blood-pressure decreases apparently depends on the ability of the rest of the body to compensate for the fluid loss. The variable results following the removal of the ligature are due to damage to the tissues in the involved area and the passage of toxic products from the injured tissues into the general circulation.

The primary factors involved in these experiments—(a) stagnation of circulatory fluid; (b) damage to large areas of tissue in such a manner that their mechanism for controlling fluid exchange and, when the area is large enough, volume is impaired, and (c) toxic products of cell metabolism and cell disintegration, may all be of importance in the production of some of the conditions which the surgeon calls shock.

In such experiments it is difficult to make estimations of the relative capacity of the capillary and venous beds involved to the total capacity of all these beds in the body. However, it was possible to obtain approximate data on the relation of the total weight of tissue below the ligature to the total body weight. This was done in animals not subjected to ligation in order to eliminate the possibility of changes in the tissues themselves as the means of complicating the results. The animals had been used in other experiments and had been fasted for twelve hours before death. The limbs were amputated at the level at which the ligature was applied and a comparison of the total weight of the amputated limbs to total body weight was made. As there are several sources of error, the comparisons are only approximate. The data show that on an average 15 per cent of the total weight of the tissues of the body was involved in the ligature.

Ligation of only three limbs produced variable results. Blood-pressure was rarely lowered to a shock pressure. Section of the nerves to each limb did not seem to produce any change in the effect of the ligation.

In summarizing it may be restated that ligation of all the structures to the limbs of a dog except the major artery will usually produce all the signs of shock. The relative amount of tissues involved by these ligatures was on an average approximately 15 per cent of the total body weight. The experiments show that a circulatory impairment following venous obstruction of the return of blood from the four limbs of an etherized animal is sufficient to produce the signs of shock.

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# A BIOLOGIC CONCEPTION OF NEOPLASIA—ITS TERMINOLOGY AND CLINICAL SIGNIFICANCE\*

WILLIAM CARPENTER MACCARTY

The efficiency of the medical profession is dependent upon at least four things, that is, perfection of its conceptions, perfection of methods, accuracy of investigation, and a large amount of kinetic energy. One of the most important economic subjects which have occupied the attention of the profession and demanded perfect conceptions is that of neoplasms.

I shall not review in detail the facts<sup>15</sup> which have led to the apparently radical declaration that the conception or conceptions which the medical profession possesses of the biogenesis, histogenesis, morphology, terminology, classification, and clinical behavior of neoplasms are based on a few facts and a great amount of speculation and empiricism.

From a biogenetic standpoint, the profession has been willing to assume the "rest hypotheses" of Cohnheim,<sup>5</sup> Ribbert,<sup>28</sup> and their followers for which there has been no absolute anatomic or experimental proof.<sup>13</sup> From a histogenetic standpoint, it has been assumed that neoplastic tissues represent an abnormal state or condition of normal tissues<sup>29</sup> and, therefore, take their origin from the arbitrary three-layer stage of embryonic development,<sup>30</sup> a basis for a conception which modern biologists agree has many contradictions in nature, especially when applied to tissue regeneration<sup>26</sup> of which neoplasia is but a non-communistic phase.<sup>16</sup>

Morphologically, the cells of neoplasms of the different layers of the three-layer stage are frequently indistinguishable.<sup>19</sup> Our terminology applied to neoplasms is a mixture of ancient gross descriptions, comparison to unrelated things and names of normal tissues.<sup>29</sup> Our classifications have been made upon a histogenetic basis<sup>29</sup> with which a recent excellent authority (MacCallum<sup>14</sup>) has demonstrated his dissatisfaction by declaring that classification is not possible; he contents himself, merely, with an "arrangement" of neoplasms.

\* Presented before the Meeting of the Washington, Oregon, and Idaho Tri-state Medical Association, Seattle, Wash., 1918. Reprinted from *Am. Jour. Med. Sc.*, 1919. Copyright, Lea and Febiger, Philadelphia.

Before attempting to establish a basis for a biologic conception of neoplasms it may be well to review the opinions of some of the leading teachers of pathology. The following quotations are either direct, in the language of the authors, or literal translations:

"One can arrange tumors according to their structure and their genesis into three groups, that is, connective-tissue tumors, epithelial tumors, teratoid tumors, and cysts. It must be mentioned, however, that many tumors allow themselves to be grouped in two or even three groups" (Ziegler<sup>31</sup>).

"The classification of tumors has been made in different ways. It seems best to me to arrange them according to their histogenesis, as most authorities have done. There is, however, the difficulty that many new-growths develop from the same tissue, thereby making the number of new-growths greater than the number of normal tissues. Therefore a histological classification according to tissue relationship also recommends itself" (Ribbert<sup>28</sup>).

"At the beginning of this chapter certain broad lines of classification that have been adopted in the case of new-growths were discussed, and it then was said that the best method of classification is one which depends upon an anatomic basis subject to the great distinction of neoplasms into non-malignant and malignant. If, then, we take the two great divisions, non-malignant and malignant, and subdivide these severally into epithelial and connective-tissue groups, we shall be able to account, in one or other of them, for the great majority of tumors. It will prove of assistance, however, if at the same time we pay some attention to the classification based upon embryological data" (Lazarus-Barlow<sup>12</sup>).

"It is not possible to-day to make a satisfactory scientific classification of tumors; but the fact that they are composed of structures which resemble the various morphologic types of tissues found in the normal body suggests a grouping of the various forms which may be regarded as a useful and suggestive catalogue. It should be remembered that the usual separation of the normal tissues into groups is useful, rather because it facilitates their study than because it expresses absolute and fundamental distinctions; and the same may be said of all the classifications of tumors. An increase of our knowledge concerning their structure and genesis will doubtless lead to a more accurate grouping of tumors, but for the present such an arrangement as that indicated below will be found of practical value for the progress of study. The attempt has often been made to classify tumors with reference to the developmental

history of the tissues represented, and it has been generally believed that cells once differentiated in the primary embryonic layers cannot again be merged in type. While this principle holds good in general, especially for highly differentiated forms, certain recent studies have seemed to indicate that even this distinction may not be inflexible. However this may be, it is certain that the cells derived from one embryonic layer may, under special conditions, come so closely to resemble in morphology those of another layer, that a structural differentiation, with our present resources at least, is not always possible. While, therefore, this, which is called the histogenetic principle of classification, is most suggestive and may be useful in connection with other data in the study of tumors, it seems to the writers that it is wiser for the present not to base our classifications too largely upon embryologic data in several particulars still subject to controversy" (Delafield and Prudden<sup>8</sup>).

"The imperfect state of our information concerning the ultimate cause of the various forms of tumors makes the matter of classification difficult; and while numerous systems have been proposed the test of increasing knowledge has shown weak points in them all. It must not be forgotten, however, that the present classification and terminology are largely artificial, and that insensible gradations occur which unite the varieties of tumors so as to leave no definite line of separation. Since the time of Virchow's classic production a vast amount of information upon tumors in their various aspects has been recorded and to this fund of knowledge each passing year makes its contributions. Paradoxical as it may seem, however, our increasing knowledge has in certain directions only served to make more confusion, and in one particular direction, viz., as regards the cause of tumors in general, speculation is as rife and almost as fruitless as it was before the modern era. Without a clear conception of all the factors which lie at the beginning of tumor formation it is not possible sharply to define them. How difficult the matter of definition is can best be illustrated by noting the fact that almost every prominent authority upon tumors has given a definition differing from that of others working in the same direction" (Hektoen-Riesman<sup>11</sup>).

"The question is: Can the histogenetic conception, in spite of the uncertainty of observations, be used as the principle of classification of tumors? Yes. At this time a combined morphologic and histogenetic conception for the classification of tumors recommends itself to me. However, one must also take biologic relations into consideration" (Borst<sup>3</sup>).

"So great is the diversity of structure in tumors, so uncertain, in many cases, is the histogenesis, that a classification based, as is the classification of the normal tissues, on structure and histogenesis presents great difficulties" (Councilman<sup>7</sup>).

"Tumors are classified, like normal tissues, on a histologic basis; that is, on the differentiation of the cells composing them. When the differentiation of the cells is marked, as it ordinarily is in slow-growing tumors, a diagnosis of the nature of the tumor is usually easy. When the growth is rapid, however, the differentiation is slight and may be entirely wanting. In the latter case we may be able only to guess at the probable diagnosis from the situation in which the tumor grows, or from having for comparison with it a series of tumors of the same nature growing at all rates of speed. Sometimes, too, in a part of the tumor the cells may grow slowly so that more or less differentiation of them has had time to take place and from them the character of the growth can be ascertained. The nomenclature of tumors is very unsatisfactory. Most names were applied long ago when much less was known about tumors than now. Consequently they may have become heirlooms which are not easily cast off. Many improvements in names have been suggested and a few have been generally accepted" (Mallory<sup>25</sup>).

"Too often have theories as to the causation of these autonomous neoplasms entered into the definitions. Thus, Cohnheim defined them as 'circumscribed atypical productions of tissue from a matrix of superabundant or erratic deposit of embryonic elements.' Here we have introduced the untenable theory that all autonomous neoplasms arise from embryonic tissue which has remained latent. We are still uncertain as to the causation of these growths, and so etiology must not enter into our definition. Thus, Ziegler's definition is more satisfactory: 'a tumor is a new formation of tissue possessing an atypical structure, not exercising any function of service to the body, and presenting no typical limit of growth.' The use and limitations of the term 'atypical structure' require here a little explanation, add to which, the pure teratomas to be presently described do present a limit of growth; and so we prefer C. P. White's statement that 'a tumor proper is a mass of cells, tissues, or organs, resembling those normally present, but arranged atypically. It grows at the expense of the organism, without at the same time subserving any useful function.' Von Rindfleisch characterizes them as a 'localized degenerated excess of growth'; that is, the very excess of growth is regarded as in itself a degeneration: Birch-Hirschfeld, as



originating spontaneously, becoming separate from the physiologic tissues in their physiologic and functional relationships, as developing from the cells of the body, and possessing progressive growth: Ribbert, as 'self-confined, dependent upon the organism for their nourishment, but otherwise largely, if not quite independent, corresponding more or less but never absolutely with the tissues of the natural body, and presenting no definite limit to their growth.' Lubarsch's definition is closely allied: 'under tumor proper we have to understand those growths of apparently independent origin which histologically correspond in structure more or less completely with the matrix from which they originate, but in form are atypical; which further, in spite of their organic connection with that matrix, and in subjection, apparently, to laws of their own, pursue an independent existence which is not, or only exceptionally, of advantage to the organism as a whole' (Adami<sup>1</sup>).

The last authoritative writer (MacCallum), in text-book form, upon the subject of neoplasms is perhaps the most conservative. He expresses a certain conciliatory attitude with the insufficiency of scientific knowledge and clearly generalizes in a manner which will be productive of future progress. "Rather than assume too accurate a knowledge of the ultimate derivation of the tumors, I have preferred to arrange them according to the general character of their tissues, both anatomic and biologic, and their form. The following list is mainly for convenience in summarizing the various forms as they have been considered here. It is an arrangement, not a classification" (MacCallum<sup>14</sup>).

These quotations, representing the best opinions upon the status of the conception of neoplasms, may be supplemented by the following list of expressions which have been utilized in the literature relating to neoplasms:

Thus authorities have stated that neoplasms represent: A specific tumor diathesis; a nutritional disturbance of the equilibrium of vegetative and functional cell power; a change between the relation of nerves to cells; a reduction of the avidity of the body cell; a primary emancipation of cell-growth from the normal laws of growth; as cellular atavism; a return to the embryonic condition of cells; an inherited or acquired intracellular abnormal metabolism; a cessation of the regulating growth influence of cell differentiation; an inherited pathologic quality of cells;

\* This list of tumors need not be published here because those who are interested in the details which have led up to these generalizations will of necessity examine the subject more thoroughly.

a failure of cells to differentiate; a disturbance of the idioplastic formation of cells; the formation of a "new race of cells"; a prenatal separation of cells; a postnatal separation of cells; a primary inherited change in the nature of cells; a change in the biologic behavior of cells; a product of connective-tissue senility; an heteroplastic change of the fixed connective-tissue cells; a congenital anlage; a release of the organic connection of cells; a separation of germinal cells; an embryonic separation of cells; a shunting of germ cells from their normal relations without misplacement; superfluity in the development of cells or tissues; separated germ cells; misplacement of cells; an abnormal persistence of embryonic cells.<sup>6</sup>

The multiplicity of diverse explanations in itself indicates dissatisfaction with the lack of accurate or scientific knowledge which we possess relative to the condition.

In the midst of such chaos one great and dominant generalization stands out. It is uppermost in practically all minds of the medical profession in all lands and forms the main basis of opposition to any new conception, which is in any way contradictory to it, that is, in 1877 Cohnheim<sup>5</sup> said, in his *Vorlesungen über allgemeine Pathologie*, "I believe that this process, referring to the embryonic development of the *monstra per excessum*, such as superfluous fingers, giant children, giant adults, giant extremities, etc., is not only confined to this field, but also applies to a much wider and more important field, namely, the field of true neoplasms."

In these words we find a generalization from a speculative correlation of some facts in the form of an hypothesis put forth by a great teacher for the inspiration of his students. Such hypotheses, although they may be proved later to be incorrect, are certainly means of correlation for future observations. In fact, it was a search for some justification for the hypothesis of Cohnheim which led to the following observations and generalizations.

Before proceeding to a presentation of the facts which form the basis of a biologic conception of neoplasms it may be well to answer the question: What should constitute a perfect conception of neoplasms?

1. We should know the cells from which neoplasms develop, since every living thing evolves from something living.

2. We should know what occurs to make some of the cells of neoplasms resemble normal tissues.

3. We should know the morphology of the component units of neoplasms.

4. We should have, if possible, a definite descriptive terminology which possesses biologic, histologic, and morphologic significance.

5. We should have a classification based upon biologic, histologic, and morphologic facts and their clinical significance for economic purposes.

6. We should be able to prognosticate the clinical behavior of neoplasms, or at least know definitely why we cannot accurately prognosticate since negative knowledge is often as valuable as positive knowledge.

7. We should know both the biologic and specific causes for the development of neoplasms.

In 1909 the writer<sup>18</sup> and <sup>20</sup> undertook an investigation of pathologic conditions in the breast with the hope of proving or disproving any relationship between chronic mastitis and carcinoma. In so doing the problem of the histogenesis was uppermost. In conducting this investigation 1000 breasts, including all chronic pathologic conditions, were studied. Many sections were made from all portions of the gland, including both normal and pathologic portions. These sections were not only submitted to microscopic study, but were studied photographically. Carcinoma being a growth which is intimately associated with glandular cells, it was thought best to study such cells in the structural and functional unit (acinus) of the organ. It was found that the unit or acinus was lined, in the resting condition and that of chronic mastitis, by two layers of cells, their inner layer consisting of cuboid or columnar cells and the outer of spheroid or ovoid cells, the latter lying adjacent to the mammary stroma.

The embryologic origin of these two layers was studied and it was found that both were derived by means of a hyperplasia and downward growth of the cells from the stratum germinativum of embryonic skin.<sup>20</sup> It was, therefore, supposed that the outer layer was the stratum germinativum of the secretory cells of the acinus. Photomicrographs of acini from all portions of the glands grouped themselves into three distinct histologic groups (Fig. 429). They were called primary, secondary, and tertiary cytoplasia respectively.<sup>20</sup>

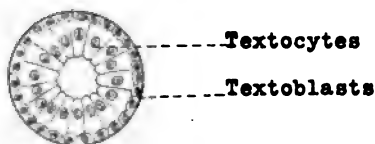
The clinical significance of these histologic pictures has been of great economic importance to the clinician, surgeon, and the pathologist. The first certainly is a benign condition, the third is, without question, the condition which has been recognized as carcinoma, and the second is not so easily interpreted; it was, therefore, spoken of as questionable in spite of the fact that the intra-acinic cells are frequently identical morpholog-

ically with the cells of the third condition.<sup>20, 21</sup> At the time of preliminary investigation I had confidence in the old criterion for histologic malignancy which utilizes the basement membrane (*membrana propria*) as the line of demarcation between a malignant and a benign condition; the cells of secondary cytoplasia are within the histologic bounds of benignancy, despite the fact that they are morphologically identical with those of carcinoma. From a clinical or practical standpoint, I have been convinced that all mammary gland-bearing tissue presenting such a picture should be removed, leaving, perhaps, the pectoral muscles and axillary lymphatic glands. I have not felt justified in advising the removal of the breast, muscles, and axillary glands by means of a radical operation. Rules have been established on this basis and subsequent post-operative histories have justified, so far, the legitimacy of such a conservative operation.<sup>22</sup>

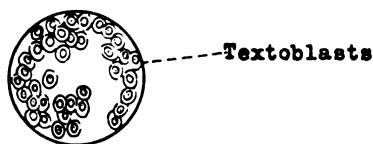
The three conditions, however, are of greatest interest from a biologic standpoint,<sup>16, 17</sup> since they furnish an opportunity for the study of the relations of cytostructure and relationship to cytofunction. From this point of view it has been clearly seen that nature has provided reserve cells (the cells of the outer row) for the secreting cells (the cells of the inner row), which in the course of their existence as a part of the communistic organism might be destroyed. These reserve cells (textoblasts) form the outer layer which is so much in evidence in chronic mastitis, which is a definite destructive condition.

The three histologic pictures represent hypertrophy, hyperplasia,

#### PRIMARY CYTOPLASIA



#### SECONDARY CYTOPLASIA



#### TERTIARY CYTOPLASIA

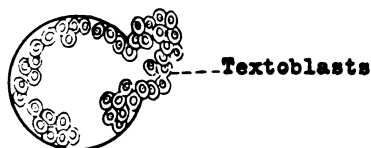


Fig. 429.—Diagrammatic representation of the original structural facts found in the mammary acinus. In primary cytoplasia the milk-producing cells (lactocytes) belong to the general group of tissue-cells (textocytes). The regenerative cells which constitute the stratum germinativum for the lactocytes have been called lactoblasts and belong to general reserve cells of the body which have been called textoblasts.

In secondary cytoplasia the lactocytes (textocytes) have disappeared and there is an hyperplasia of the lactoblasts (textoblasts).

In tertiary cytoplasia the lactoblasts (textoblasts) have migrated (in a biologic sense) from their normal acinic habitat.

and migration, which are the fundamental protective activities of all living matter throughout nature, the first representing hyperactivity, the second reproduction, and the third change of environment. The biologic cause of this apparent sequence of cytoaction is undoubtedly destruction or the presence of a destructive agent or agents. Some thing or some environmental condition, or both, call forth protective hyperactivity on the part of the textoblasts. In the second histologic picture actual, partial, or complete destruction of textocytes calls forth a hyperplasia or reproduction of textoblasts. Although the destructive

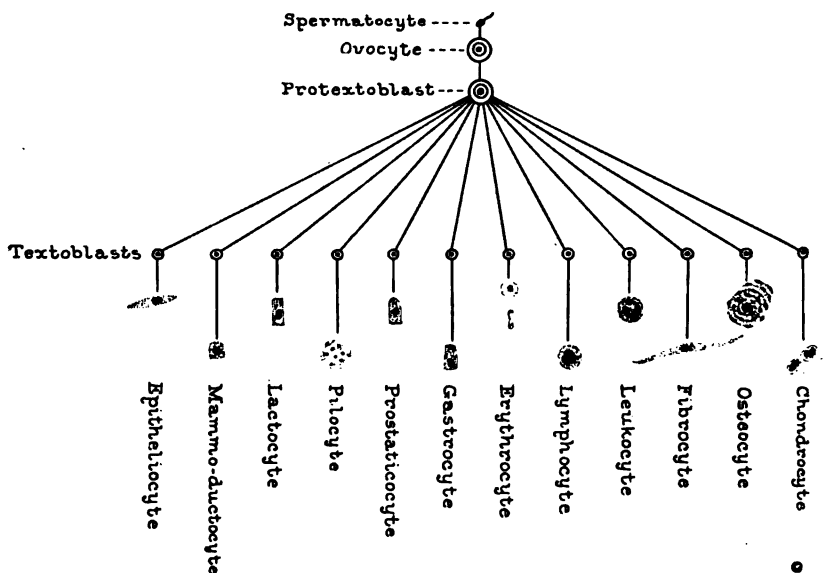


Fig. 430.—Diagrammatic representation of the embryologic evolution of the tissue-cells (textocytes) the reserve cells (textoblasts) of which have been studied.

After fertilization of the ovocyte, the biologic phenomena of segmentation, prodifferentiation, and differentiation occur. The cells produced during these phenomena have been called protetoblasts, textoblasts, and textocytes. This diagram represents the second stage in the evolution of the structural basis for a biologic conception. Fig. 429 is the first stage and Fig. 431 is the third stage.

factor is unknown, it is of sufficiently low virulence not to destroy the reserve cells, and sufficiently virulent to prevent their complete differentiation and specialization into textocytes. The textoblasts remain spheroid or ovoid and do not remain in their normal acinic arrangement, although they may still retain their acinic habitat.

During all investigations no attention was paid to the specific agent or agents causing these reactions, because it was thought best to study primarily the biologic factor or factors.

The three fundamental biologic reactions to destruction have been found to occur not only in relation to the specific tissue of the breast,

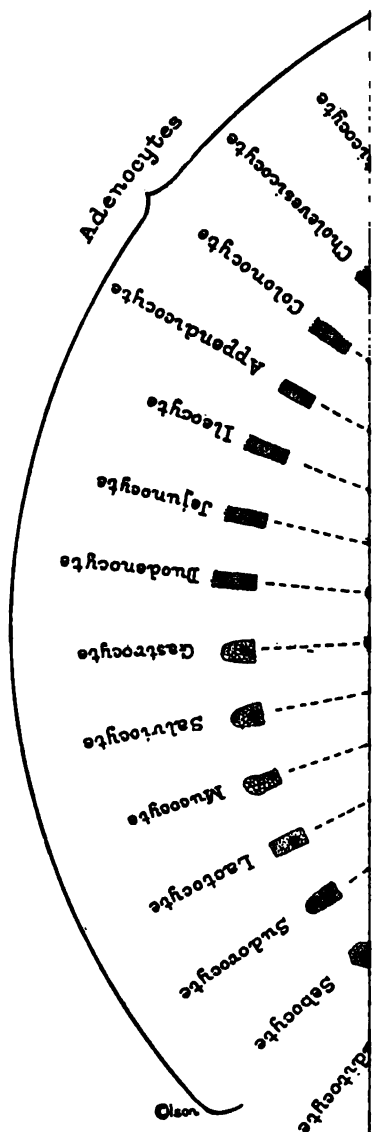


Fig. 491.—Diagrammatic representation of the body probably do not possess cell in order to emphasize the factor of tissue. No attempt has been made to draw per body is composed of distinctly specialized structural and functional characteristics can



but also in relation to the specific tissues of the prostatic gland, skin, hair-follicles, stomach, lymphatic glands, blood, bone, cartilage, and connective tissue.<sup>2</sup> In all these chronic destruction of the specific tissues calls forth hypertrophy, hyperplasia, and sometimes migration of the reserve cells.

Although these reactions may seem new in reference to human pathology, they are well known to biologists who have made a study of reaction to destruction. In fact, many biologists are of the opinion that exposure of living matter to destructive factors has led to such adaptive potentialities that are the factors of safety in the structure and function of all forms of life; nature has been just as efficient in her defensive preparation in the construction of the human body.

It may be stated as a biologic law that hypertrophy, hyperplasia, and migration are stimulated primarily by destruction. These phenomena are the effects of which destruction is the cause.

In nature the specific agent of destruction is rarely if ever anticipated. It makes no difference whether the leaf, stem, or branch of a geranium plant is pinched off, broken off, cut off, eaten off, or burned off—the main factor is the destruction. In the mammary gland destruction is the main factor, as it is with the other tissues which have been studied.

The reactionary cells of the three conditions described above are apparently normal cells which answer the structural description of normal cells as found any place in nature. Their relation to the communistic organization of cells is their principal abnormal or pathologic characteristic.

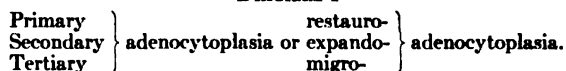
Many authorities have considered the cells of neoplasms to be intrinsically and structurally abnormal without positively demonstrating that such cells are even structurally abnormal. Practically every authority, including biologists, who speaks or writes upon the subject of abnormality of neoplastic cells quotes Hanseemann<sup>9</sup> and Galeotti,<sup>10</sup> who described atypical mitoses and other unusual conditions in the cells of malignant neoplasms. As a result of my own failure to find in perfectly fresh and unfixed cells such atypical mitosis as a characteristic of neoplastic cells it has seemed that the basis of irregular mitosis as described by the authorities mentioned is probably not so much a question of their actual occurrence as it is a question of their being due to artefacts, poor fixation, unusual planes through mitotic figures, or swollen, distended, or disintegrating cells. The work of Hanseemann and Galeotti might well be repeated, utilizing perfectly fresh, unfixed material, the cells of which should be studied from the standpoint of orthographic projection and cellular disintegration.



In so far as cancer (a migratory hyperplasia) is concerned, my observations have revealed a biologic reaction which is malignant only insofar as it destroys the communistic organization of cells.

In all the tissues which have been studied there is a normal reserve stratum or focus, the cells of which exist in a partially differentiated or undifferentiated condition. In the human body, however, some primitive tissues possessing reproductive potentiality exist. The cells of the nervous system, muscular system, endothelial system, and perhaps the cells lining the alimentary canal and others belong to this group. This may account for the failure to find the reserve cells for some of the specific tissues of the body. Whether or not there be reserve cells does not alter the biologic phenomena, because all cells possessing the power of regeneration react in the same way. Under certain conditions of destruction such cells become hypertrophic, hyperplastic, and migratory. These phenomena, which are very evident in the reactions of cells of the body and in the rest of nature, demand descriptive names.<sup>24</sup> As has been stated, they have been called primary, secondary, and tertiary reactions or conditions (cytoplasias). It seems logical to attempt to describe the reactions of certain tissues by adding the root of the name of the reacting tissues—thus the conditions in the glandular epithelium (adenotex) of the breast were described as:

DIAGRAM 1



This terminology expresses the biologic phenomena, the histologic pictures, and cytologic conditions of cytodifferentiation of a specific tissue without stating the stage of cytodifferentiation. Primary adenocytoblastia represents the ordinary attempt at restoration of the specific glandular tissue; secondary adenocytoblastia represents an expansive overgrowth of the reserve cells of the glandular tissue, and the tertiary adenocytoblastia represents a migratory hyperplasia. The first condition is clinically a benign reaction, since it is but the process of repair; the second is uncertain as to benignancy or malignancy because no one can foretell whether the hyperplastic undifferentiated cells will become differentiated into specific tissue cells or become migratory and eventually destroy the organism.

Such a conception of neoplasia with its terminology, insofar as this one tissue is concerned, seems very simple and certainly useful.

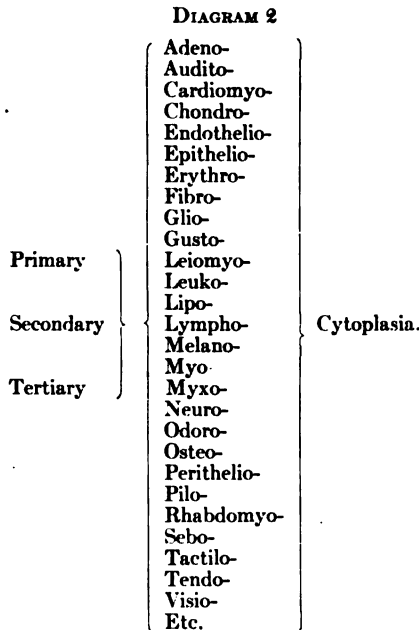
In view of the fact that this conception is biologically logical and expressive of what actually happens in the evolution of this one tissue

the accompanying diagram has been constructed for all tissues that have been studied (Diagram 2).

Instead of adhering to the old idea of classifying tissues into epiblastic, mesoblastic, and hypoblastic tissues, as the text-books have done, it seems that the human body is made up of as many specific and differentiated tissues as there are different kinds of cells with different morphology and function in the body. As a result of structural and functional segmentation of the fertilized ovum there arise many tissues which deserve just as much recognition as entities as do the specific tissues described in text-books of histology.

One cannot make progress in constructing a biologic conception of neoplasia unless all the known tissues receive names and have their morphologic and perhaps functional characteristics appreciated. It has, therefore, been deemed essential to name these tissues and establish their biologic relationships. Based on their morphology and function, each tissue should receive a name (Diagram 3) which differentiates it from all other tissues in the body and makes it an entity to be dealt with from the standpoint not only of morphology and function, but of cytoregeneration and differentiation, certain phases and combinations of which produce benign or malignant neoplastic conditions.

The three reactions may be expressed, therefore, as follows:



There is one other important phenomenon in connection with cytoplasia to be described, that is, cytodifferentiation. Insofar as the human organism is concerned the cells which constitute the tissues are differentiated in three degrees during their evolution. The textoblasts which are to form tissues first arrange themselves according to the general direction of the adult tissue (primary differentiation); if the textocytes are to cover a surface, the textoblasts arrange themselves first in a plane; if they form an acinus, they arrange themselves in the form of the lining surface of an acinus. In the first stage or primary differentiation the cells are still undifferentiated insofar as their morphology is concerned. The second stage (secondary differentiation) consists of the establishment of tissue cytopolarity (textocytopolarity) and the third (tertiary differentiation) consists of normal alignment, normal polarity, and normal appearance of cytoplasm and nucleoplasm. Complete differentiation (the third degree) plus normal function produces an accessory tissue, or if more than one tissue be involved, an accessory organ.

This phenomenon of differentiation is not only one which is seen during the evolution of normal tissues, but one which plays an important rôle in the evolution and life-history of neoplasms.

If the cells of the stage of cellular regeneration (cytoregeneration, which has been called secondary cytoplasia) become differentiated to the third degree, a benign neoplasm is formed. It is thus that fibromas, adenomas, fibromyomas, adenomyomas, and other benign neoplasms occur. There is an expansive overgrowth of the fibro-, myo-, and adenoblasts, which become differentiated either separately or in combination to the point of morphologic identity with their respective textocytes. It is true that in many such neoplasms the process of expansive overgrowth continues gradually by virtue of the existence of some remaining textoblasts, which become readily differentiated.

In some conditions of secondary and migratory cytoplasia differentiation does not occur, or at least never reaches beyond the first and second stages. This is true of the so-called malignant neoplasms. Complete differentiation is apparently impossible. If it occurred in tertiary cytoplasia, accessory tissues would appear in malignant neoplasms.

Upon examination of tissues, insofar as cytoregeneration and differentiation are concerned, one must determine the following facts:

DIAGRAM 3

LOCATION	GROSS FORM	BIOLOGIC AND CLINICAL REACTION	TISSUE INVOLVED	THE DEGREE OF DIFFERENTIATION
capito- collo- cranio- auriculo- naso- linguo- labio- laryngo- etc.	circumscribed diffuse cystic extracystic intracystic ductal intraductal periductal papillary polypoid ulcerated	{ Primary Secondary Tertiary }	{ audito- adeno- cardiomyo- chondro- endothelio- epithelio- erythro- fascio- fibro- glio- gusto- leiomyo- leuko- lipo- lympho- melano- myo- myxo- neuro- odoro- osteo- perithelio- pilo- rhabdomyo- sebo- tactilo- tendo- visio- x-	cytoplasmia with or without { Primary Secondary Tertiary } differentiation

The terminology which is expressive of these facts may be abbreviated in the following manner:

DIAGRAM 4

LOCATION	GROSS FORM	DEGREE OF BIOLOGIC AND CLINICAL REACTION	TISSUE	DEGREE OF DIFFERENTIATION
capito- collo- cranio- auriculo- naso- linguo- labio- laryngo- etc.	{ circumo- diffuso- cysto- extracysto- intracysto- ducto- intraducto- extraducto- papillo- polypo- ulcero-	{ (1) (2) (3) }	{ audito- adeno- cardiomyo- chondro- endothelio- epithelio- erythro- fascio- fibro- glio- gusto- leiomyo- leuko- lipo- lympho- melano- myo- myxo- neuro- odoro- osteo- perithelio- pilo- rhabdomyo- sebo- tactilo- visio- x-	cytoplasmia (1) (2) differentiation. (3)

These same facts may be symbolically expressed in the following manner:\*

capito-	(Δ)	(Au)
collo-	(Λ)	(Ad)
cranio-	(O)	(Cm)
auriculo-	(θ) (1)	(Ch) (1)
naso-	(Φ) (2)	(En) (2) D.
linguo-	(Τ) (3)	(Ep) (3)
labio-	(Π)	(Er)
laryngo-	(Ψ)	(Fa)
etc.	(Ρ)	(Fi)
	(Ω)	(Gl)
	(Σ)	(Gu)
		(Lm)
		(Le)
		(Li)
		(Ly)
		(Me)
		(My)
		(Mx)
		(Ne)
		(Od)
		(Os)
		(Pe)
		(Pi)
		(Rm)
		(Se)
		(Ta)
		(Te)
		(Vi)
		(X)

This symbolic terminology has been utilized on account of brevity and accuracy in expressing the facts relative to regeneration in its relation to neoplasia. If one wishes to describe what has been called a fibro-adenoma of the breast, it may be written: Mammo 2Δ (fi ad) 3D which expresses, to one familiar with the key, the location, gross form, degree of cytoplasia, tissues involved, and the degree of cytodifferentiation.

\* In this key the root of the accepted His anatomic nomenclature expresses the organic location; the Greek capitals represent the gross form or manifestation of the neoplastic condition; the numerals 1, 2, and 3 indicate the biologic stage of cyto-activity (hyper-trophy, hyperplasia, and migratory hyperplasia); the first two letters of the roots of accepted names of specific tissues are utilized symbolically in a similar manner to that utilized in chemical symbolic terminology; the numerals 1, 2, and 3, before the capital D, express the degree of differentiation. The Greek letters have the following symbolic meaning:

Δ delta	= circumscribed or encapsulated
Λ lambda	= diffuse or non-encapsulated
Ο omicron	= cystic
θ theta	= intracystic
Φ phi	= extracystic
Τ tau	= ductal
Π pi	= intraductal
Ψ psi	= extraductal
Ρ rho	= papillary
Ω omega	= polypoid
Σ sigma	= ulcerated

Malignancy and benignancy depend on at least two factors insofar as the tissues and their reactions are concerned. These are the biologic reactions of hypertrophy, hyperplasia, migration, and degree of cyto-differentiation. Undoubtedly there are other factors, such as lymphocytic infiltration, fibrosis, hyalinization, location, encapsulation, and perhaps conditions which are as yet unknown, but these factors are not sufficiently understood to be placed in our present terminology.

The main facts in any compound terminology are universality, simplicity, accuracy, brevity, and expressiveness of structural and functional facts and relationships. In the compound terminology just expressed structure, characteristic functions, biostructural relationships, and clinical values are briefly, systematically, simply, and accurately portrayed. This, unfortunately, cannot be said of the compound and simple terminology which is expressed in text-books, taught to twentieth century students and practised by pathologists in all parts of the world. This new terminology is perhaps not perfect any more than Lavoisier's improvements in chemical terminology were perfect, but it is an improvement and will serve as a basis for more perfect terminology in the future.

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# TUBERCULOSIS ASSOCIATED WITH MALIGNANT NEOPLASIA: REPORT OF 20 CASES\*

A. C. BRODERS

To Rokitsky has been given the credit for teaching that tuberculosis and cancer are incompatible diseases, but since McCaskey, in 1902, made the statement that he was strongly inclined to doubt that Rokitsky had ever held to this extreme view, it may be well to quote direct from Rokitsky's article on cyst formation:

"Cyst formation, as a new growth, is rarely found concurrent with tubercle, either in the same organ or in the same organism generally." With regard to tuberculosis and cancer he said:

"A similar antagonism, as shown from still more numerous observations, prevails between tubercle and carcinoma. Whenever their general correlation is susceptible of proof, cancer has seemed to succeed to tuberculosis, tubercle rarely to become developed after the extinction of cancer and its crisis," and also:

"A corresponding result of much interest is afforded by a comparison of the scale of frequency of cancer and tubercle, as well as of several special local relations of both. They are diametrically opposed to one another, as thus:

FREQUENT	RARE
Lung tubercle	Lung cancer
Ovarium cancer	Ovarium tubercle
Salivary gland cancer	Salivary gland tubercle
Stomach cancer	Stomach tubercle
Esophagus cancer	Esophagus tubercle
Rectum cancer	Rectum tubercle
Ileum tubercle, etc.	Ileum cancer, etc."

From the foregoing it is obvious that Rokitsky did not teach that the two diseases are incompatible, but that an antagonism prevails. While a few writers have held to the view that an antagonism exists between active tuberculosis and cancer, by far the greater number are of the opinion that no antagonism exists. McCaskey is apparently inclined

\* Reprinted from Jour. Am. Med. Assn., 1919, lxxii, 390-394.



to the former view, and he has suggested the systematic local injection of tuberculin in the cancerous tissue in properly selected inoperable cases of cancer. Dabney, writing in 1916, fourteen years later, practically agrees with McCaskey. He has injected the tuberculin in seven cases of cancer, and in one improvement of the patient's general condition immediately became very marked, and this improvement continued after three months or more of tuberculin therapy. Dabney used, as a basis for his argument in favor of the injection of tuberculin in cancer cases, that it would bring about a lymphocytosis in practically all cases, and as

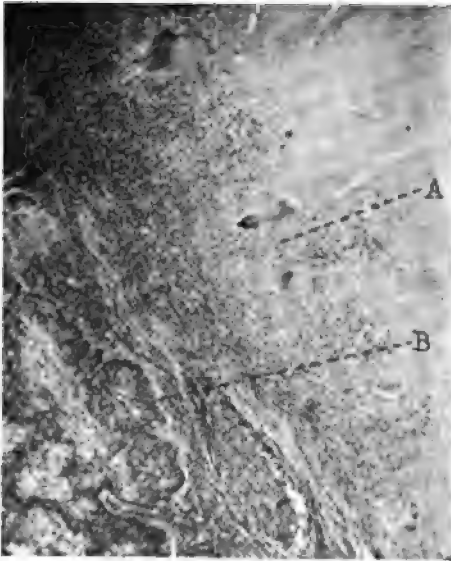


Fig. 432.—(A59139) Tuberculosis and epithelioma in lymph-gland of neck: *A*, Tuberculosis showing giant-cells; *B*, epithelioma (low power). The patient died.

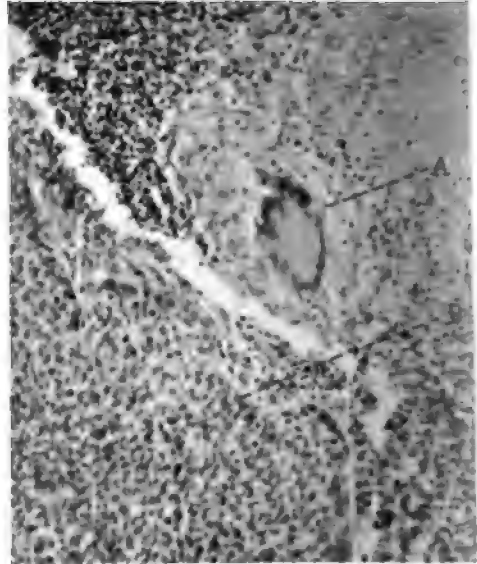


Fig. 433.—(A59139) Same as Figure 432. *A*, Giant-cell of tuberculosis surrounded by epithelioid cells; *B*, epithelioma showing numerous mitotic figures (high power).

Murphy and Morton and others have shown that lymphoid activity is an essential factor in the immunity process of artificially engrafted cancer, it would seem that the tuberculosis that brought about a condition of lymphoid activity would exert an inhibitory influence on cancer.

From time to time the negative side of this question has been most ably defended, not only by observations made at necropsy, but also from a surgical pathologic standpoint. The first and one of the most noted defenders of the theory was Lebert. Williams found a history of phthisis in 151 (47.7 per cent) of 316 cancerous families. Lubarsch, in 1888, found carcinoma in 2668 tuberculous cadavers in 117 (4.4 per

cent) instances, and in 3868 non-tuberculous cadavers he found the condition in 452 (11.7 per cent) instances. In 569 carcinomatous cadavers he found tuberculosis in 117 (20.6 per cent) instances, and in 5967 non-carcinomatous he found it in 2551 (42.7 per cent) instances. His statistics indicate that carcinoma is found more often in non-tuberculous than in tuberculous persons, the proportion being about 3:1 in favor of the former. He has also shown that tuberculosis is found twice as often in non-carcinomatous as in carcinomatous persons. Moak, quoting

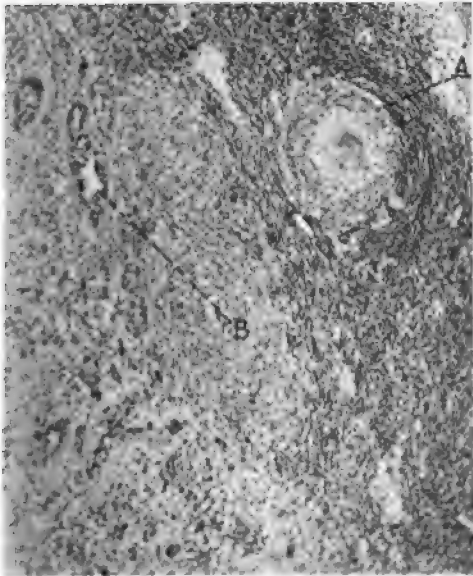


Fig. 434.—(A192320) Tuberculosis and epithelioma in lymph-gland of neck; A, Tubercle with giant-cell; B, epithelioma (low power). Patient's condition unknown.

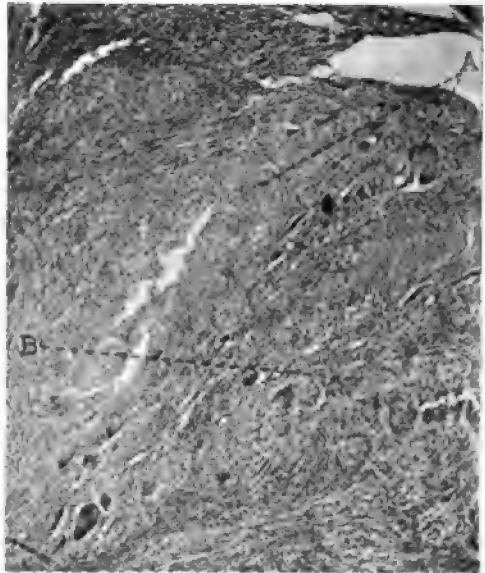


Fig. 435.—(A51290) Tuberculosis and epithelioma in lymph-gland of neck; A, Tuberculosis showing necrotic area and giant-cells; B, epithelioma (low power). Patient living and well ninety-one months after operation.

Lubarsch, mentions five possible combinations of cancer and tuberculosis:

"1. Simple coincidence. The diseases having no apparent action the one upon the other.

"2. Metastatic carcinoma developing secondarily upon a recent or old tuberculous focus.

"3. A tubercular infection becoming engrafted on a cancer in full evolution.

"4. Chronic progressive tuberculosis on which develops a cancer.

"5. The simultaneous development of both cancer and tuberculosis."

Naegeli, in 420 necropsies on adults of more than eighteen years, showed that 93 per cent had either active, latent, or healed tuberculosis.

Hoffman's statistics show that in the United States registration area for the year 1913, out of 93,293 deaths from tuberculosis, 73.39 per cent occurred at ages under forty-five and 26.61 per cent at ages over forty-five and that of 49,887 deaths from cancer at all ages, 15.46 per cent occurred at ages under forty-five and 84.54 per cent at ages over forty-five.

*Anatomic location of tuberculosis and cancer.*—Rokitansky and others have pointed out that these conditions are rarely found combined in certain

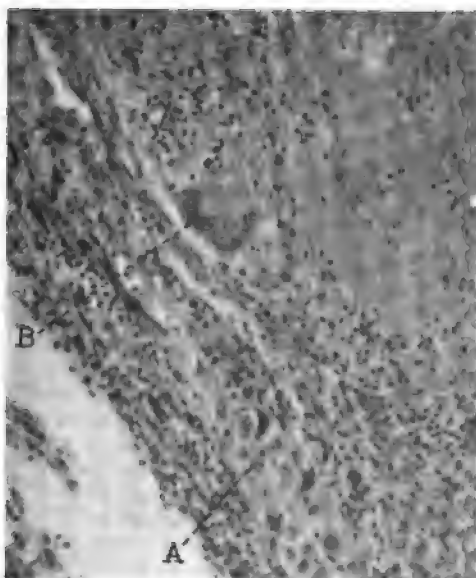


Fig. 436.—(A51290) Same as Figure 435. A, Epithelioma cells; B, giant-cell of tuberculosis (high power).

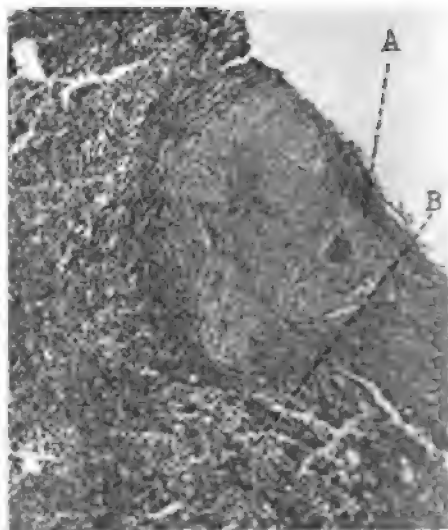


Fig. 437.—(A72500) Tuberculosis and lymphosarcoma in lymph-gland of neck: A, Tubercle with giant-cell; B, lymphosarcoma cells (low power). Condition of patient unknown.

organs, such as the esophagus, stomach, ileum, rectum, salivary glands, lungs, ovary, thyroid, pancreas, etc. I was able to find but five positive and probable cases in which tuberculosis and cancer of the stomach were combined. The two diseases, in most instances, seem to select different anatomic points of origin, and by a metastatic process through the lymph- or blood-stream they meet at the starting-point of one or the other, or at some point remote from their field of origin, such as the lymphatic glands.

Why one tissue or organ should be susceptible to malignant neoplasia or tuberculosis and another should be, to a great extent, immune is difficult to explain; nevertheless, such seems to be an established fact.

Tuberculosis associated with sarcoma has been reported by Ricker, Trendweiler, and Iscovesco (Moak). Tuberculosis associated with connective-tissue malignant neoplasia is rare; the records of the Mayo Clinic show that epithelial tissue malignant neoplasia is about nine times as frequent as connective-tissue malignant neoplasia. As an indication of the frequency of the association of tuberculosis with malignant neoplasia, statistics are cited both from necropsy and surgical pathologic standpoints as in Table 1:

TABLE 1  
CASES FROM THE LITERATURE OF THE RELATIONSHIP OF TUBERCULOSIS AND CARCINOMA AT NECROPSY

AUTHOR	CARCINOMA	ASSOCIATED TUBERCULOSIS	PER CENT
Cohen.....	257	13	5.0
LeGoupils.....	632	53	8.4
Loeb.....	111	31	27.9
Lubarsch.....	569	117	20.6
Rapok.....	399	39	9.8
Sandu-Miclesco.....	150	14	9.3
Schrader.....	50	8	16.0
Williams.....	166	27	16.2
	1445	236 Average	16.3

*Cases from the literature found by the surgical pathologist or at necropsy.*  
—Naegeli reported three cases in which tuberculosis and carcinoma were associated. The first patient had carcinoma and tuberculosis of the rectum, the second carcinoma and tuberculosis of the ileum, and the third colloid carcinoma and tuberculosis of the cecum.

Warthin reported two cases of carcinoma and primary tuberculosis associated in the mammary gland; in the second case both diseases were in the axillary glands also.

Crowder reported a case of tuberculosis and carcinoma of the cecum with tuberculosis of the lungs, peribronchial and retrocecal lymph-glands.

Moak reported five cases of associated tuberculosis and carcinoma. The first case is practically the same as Warthin's second case: the primary tuberculosis and carcinoma in the mammary gland were associated with both diseases in the axillary glands. In the second case metastatic carcinoma was associated with tuberculosis in an axillary lymph-gland. In the third, carcinoma of the mammary gland was asso-

ciated with carcinoma and tuberculosis in a lymph-gland, probably from the axilla. In the fourth, adenocarcinoma was associated with tuberculosis in the sigmoid flexure, and the same combination was in the liver and the left kidney. The fifth case showed an adenocarcinoma and tuberculosis of the lungs, bronchial glands, retroperitoneal hemolymph glands, suprarenal, liver, and spleen, secondary to primary carcinoma of the prostate and primary tuberculosis of the lungs. Moak quotes Steinhäuser as having collected from the literature 83 cases of lupus and carcinoma of the skin and reported five new cases. Prior to the publication of the articles of Naegeli, Warthin, Crowder, and Moak, 1897, 1899, 1900, and 1902, respectively, a fairly large number of cases showing the association of the two conditions were reported, particularly in Europe, and since that time a fairly small number have appeared both here and abroad.

TABLE 2  
CASES STUDIED IN THE SURGICAL PATHOLOGIC LABORATORY OF THE  
MAYO CLINIC

Cases.....	20
Males.....	14 (70 per cent)
Females.....	6 (30 per cent)
Average age.....	49 years
Oldest.....	77 years
Youngest.....	20 years
Family history of malignancy.....	2 (10 per cent)
Family history of tuberculosis.....	3 (15 per cent)
Personal history of tuberculosis.....	3 (15 per cent)
Epithelioma of the lip.....	7
History of smoking.....	2 (28.5 per cent)

#### TYPES OF MALIGNANT NEOPLASMS

Squamous cell epithelioma.....	13 (65 per cent)
Melano-epithelioma.....	1 ( 5 per cent)
Adenocarcinoma.....	5 (25 per cent)
Lymphosarcoma.....	1 ( 5 per cent)
Average duration.....	21.5 months
Average greatest diameter.....	4.2 cm.
Greatest diameter.....	15 cm.
Smallest diameter.....	1 cm.

#### PRIMARY LOCATIONS OF MALIGNANT NEOPLASMS

Lip.....	7 (35 per cent)
Cheek.....	3 (15 per cent)
Breast.....	2 (10 per cent)
Near angle of jaw.....	2 (10 per cent)
Ear.....	1 ( 5 per cent)
Nose.....	1 ( 5 per cent)
Neck (lymph-glands).....	1 ( 5 per cent)
Parotid gland.....	1 ( 5 per cent)
Transverse colon.....	1 ( 5 per cent)
Rectum.....	1 ( 5 per cent)
Total with metastasis.....	11 (55 per cent)
Total without metastasis.....	9 (45 per cent)

TABLE 2.—(Continued)

## LOCATIONS OF METASTATIC NEOPLASMS

Lymph-glands of neck.....	9 (81.8 per cent)
Lymph-glands of axilla.....	2 (18.2 per cent)

## METASTASES TO NECK: PRIMARY LOCATIONS

Lip.....	4 (44.4 per cent)
Cheek.....	2 (22.2 per cent)
Ear.....	1 (11.1 per cent)
Nose.....	1 (11.1 per cent)
Neck.....	1 (11.1 per cent)

## METASTASES TO AXILLA: PRIMARY LOCATION

Breast.....	2 (100 per cent)
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## LOCATIONS OF TUBERCULOUS PROCESSES

Lymph-glands of neck.....	15 (75 per cent)
Lymph-glands of axilla.....	2 (10 per cent)
Lymph-glands of mesentery.....	1 ( 5 per cent)
Omentum and peritoneum.....	1 ( 5 per cent)
Lip.....	1 ( 5 per cent)

## THE RELATION OF THE ASSOCIATION OF TUBERCULOSIS AND MALIGNANT NEOPLASIA

In the same organ or tissue.....	8 (40 per cent)
Lymph-glands of neck (lymphosarcoma, primary) 1	7 (87.5 per cent)
Lymph-glands of axilla.....	1 (12.5 per cent)
In the same microscopic field (low power) lymph-glands of neck.....	7 (87.5 per cent)
In the adjacent organs or tissues.....	5 (25 per cent)
Lymph-glands of the neck.....	3 (60 per cent)
Lymph-glands of the neck and the parotid gland	1 (20 per cent)
Lymph-glands of the axilla.....	1 (20 per cent)
Not intimately associated.....	7 (35 per cent)
Malignant neoplasm—Tuberculosis:	
Lip.....	Lymph-glands of neck.... 3 (42.9 per cent)
Cheek.....	Lymph-glands of neck.... 1 (14.3 per cent)
Near angle of jaw.....	Lymph-gland of neck.... 1 (14.3 per cent)
Transverse colon.....	Lymph-glands of mesentery 1 (14.3 per cent)
Rectum.....	Omentum and peritoneum. 1 (14.3 per cent)

## PRESENT CONDITION

Dead.....	4 (20 per cent)
Living.....	10 (50 per cent)
Condition unknown.....	6 (30 per cent)

Three of the four patients who died had malignant metastases in the glands of the neck.

Two of the 10 living patients have a recurrence of malignancy, 3 are in good health, and 5 have been operated on too recently to be considered. Of the 3 known to be in good health, 160 months, 91 months, and 39 months, respectively, after their last operations, the latter 2 had epithelioma and tuberculosis in the glands of the neck.

## CONCLUSIONS

1. The theory prevailing among the majority of physicians for a number of years, and still prevailing among a few, that tuberculosis and malignant neoplasia are antagonistic, has not been borne out by the facts.
2. The fact that some tissues or organs are, to a certain degree, immune from one or the other or both of these diseases does not prove that the two diseases are antagonistic.

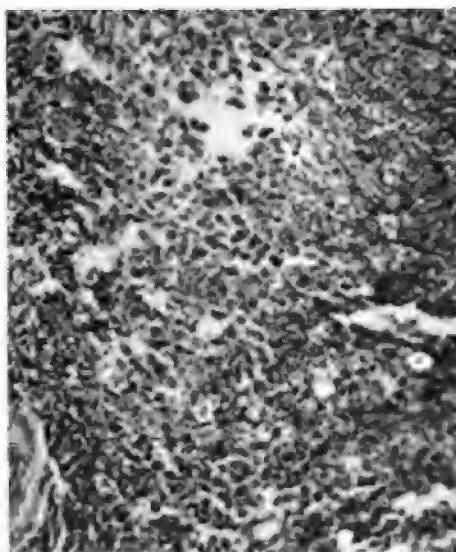


Fig. 438.—(A72500) Same as Figure 437. Lymphosarcoma cells (high power).

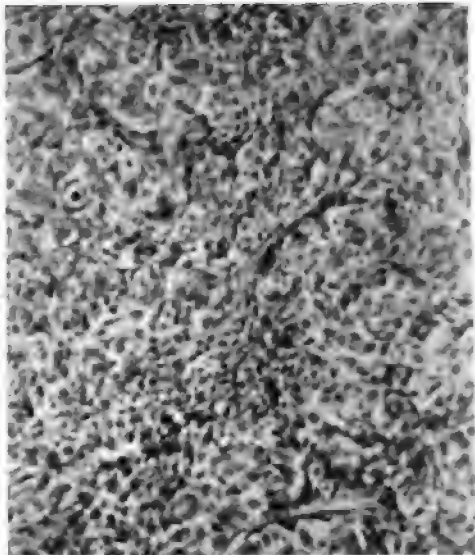


Fig. 439.—(A205751) Melano-epithelioma of lymph-gland of neck (high power).

3. If the observations of Naegeli are correct, in which he showed that in 93 per cent of 420 necropsies on adults more than eighteen years of age, either active, latent, or healed tuberculosis had been present, then it is reasonable to believe that similar findings should prevail in an equal number of persons who have died with malignant neoplasia.

4. It would seem that the reason pathologists are not finding tuberculosis more frequently at necropsy in persons who have died with malignant neoplasia is owing to the fact that the pathologists are satisfied to find the malignant neoplastic condition and, therefore, fail to make a thorough search for tuberculosis.

5. Since the surgical pathologist's examination is limited to the tissue removed by the surgeon, he is greatly handicapped in the search for the two conditions associated, while the pathologist doing a necropsy has access to a large part or the whole of the body.

6. The fact that active tuberculosis occurs most frequently in persons under forty-five, and malignant neoplasia, especially epithelial tissue



Fig. 440.—(A205751) Tuberculosis in lymph-gland, same as Figure 439, different field (low power). Condition of patient unknown.

malignant neoplasia, most frequently in persons over forty-five, does not prohibit the association of latent and healed tuberculosis with malignant neoplasia.

7. In my series of 20 cases the two conditions were associated in the same microscopic field seven times (35 per cent).

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## NEUTRAL SOLUTION OF CHLORINATED SODA (DAKIN'S SOLUTION) IN THE NORMAL PERITONEAL CAVITY

F. C. MANN AND W. G. CRUMLEY

The purpose of this research was to determine whether or not neutral solution of chlorinated soda (Dakin's solution) could be used with safety in the peritoneal cavity. The series of experiments was begun with the sole idea of deciding this point for our own benefit, as we believed that other investigators more closely associated with the work would soon publish similar experiments. Since this has not been done, we thought it might be of value briefly to give our results.<sup>1</sup>

All of the experiments were performed on dogs. In some cases the animals were etherized and the effect of the injection of the solution on the blood-pressure was noted. In other experiments the symptoms produced by the injection on the normal animal were studied.

The solution was made fresh for each day's experiments except in those cases in which it was desired to observe the effect of an old preparation, and the hypochlorite concentrate varied between 0.45 and 0.50 per cent and was neutral.

The usual effect of an intraperitoneal injection of a fresh preparation of Dakin's solution into an etherized dog is an immediate and marked drop in blood-pressure, which progresses until it becomes quite low. This result is, of course, more marked when large amounts (300 c.c.) of the solution are employed, but also occurs at times with relatively small quantities. Usually, however, when small amounts (10 c.c.) are used, the blood-pressure is at first slightly increased but is soon followed by a decrease. It may or may not return to normal (Experiments 212-17 and 253-17, and Fig. 441).

The first effect produced by the intraperitoneal injection of Dakin's solution in an unanesthetized dog is evidence of pain. This has been elicited with as small an amount as the first 2 c.c. of an injection. The

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animal develops a marked abdominal rigidity, spontaneously passes

feces and urine, vomits, and becomes very restless. When the injection has been relatively small (10 c.c.), the effects gradually decrease, and may have practically disappeared within an hour or two. When larger amounts are injected, the animal may be restless until death occurs.

At the necropsy of a dog dying after the intraperitoneal injection of Dakin's solution three changes are always noted: The peritoneal cavity and usually the pleural cavities contain a dark blood-stained fluid. There may be quite large amounts of this fluid present. The omentum and the intestine are perforated with numerous holes, and in some cases only the large blood-vessels of these structures remain. The parietal peritoneum on the side on which the animal has lain is edematous.

The effect of the injection of Dakin's solution into the pleural cavity is practically negligible both in the anesthetized and in the unanesthetized animal. Of course, owing to the mechanics of the thorax, only relatively small amounts of the solution can be injected. Blood-pressure is only slightly affected; the animal does not show signs of pain. In one dog, 20 c.c. of the solution injected into the right pleural cavity did not produce any noticeable effect, while 5 c.c. injected intraperitoneally produced a marked reaction (Experiment 290-17).

The intravenous injection of Dakin's solution in the dog is comparatively not very dangerous. Carrel and Dehelly<sup>2</sup> state that the solution is very dangerous



Fig. 441 (Experiment 288-17).—Kymograph record showing the effect of the injection of Dakin's solution on blood-pressure.

when injected into the general circulation of rabbits. The only changes noted were increased coagulation time and a laking of the blood, which assumes a very dark color. Blood-pressure is only slightly affected by doses which produce a marked reaction when injected intraperitoneally. The intravenous injection of 180 c.c. in 30 c.c. doses every half-hour did not produce any other changes except those noted as affecting the blood (Experiment 319-17).

In one series of experiments the effect of an old preparation of Dakin's solution was studied. After the usual results had been obtained with the fresh solution, the remaining portion was tightly corked in an amber-colored bottle and placed in a dark room in which the temperature was not more than 20 C. The effect of the intraperitoneal injection of a solution kept under such conditions for three or four days was practically negligible.

#### CONCLUSIONS

1. The intraperitoneal injection of various amounts of Dakin's solution in the dog produces—(a) Decrease in blood-pressure, (b) pain, (c) marked serous exudate, (d) erosion and perforation of the omentum and mesentery, and (e) with rather large amounts, eventually death.

2. The injection of Dakin's solution into the pleural cavity, in amounts too small to produce a mechanical action, is without noticeable effect.

3. The intravenous injection of Dakin's solution in amounts large enough to produce a marked reaction when injected into the abdominal cavity does not produce any general effect. When large injections are employed, the blood is laked and the coagulation time is greatly increased.

4. An amount of solution which is practically innocuous in either the pleural cavity or vascular system will produce quite marked effects when injected into the peritoneal cavity.

5. Only fresh preparations produce this response when injected intraperitoneally.

6. These conclusions apply only in regard to the action of Dakin's solution in the normal peritoneal cavity.

#### EXPERIMENTS

The most important experiments are given briefly herewith. While very large amounts of the solutions were employed in the first three experiments, only moderate amounts were subsequently used.

**EXPERIMENT 199-17.**—March 7, 1917, Dog B 835, a male brown mongrel shepherd, weighing 20.3 kg. Under cocain anesthesia and with sterile technic a small opening was made into the peritoneum in the mid-line, just above the umbilicus, and 900 gm. of a fresh preparation of Dakin's solution were passed. The animal barked and gave evidence of pain. Toward the end of the injection the lower extremities and abdominal region became cyanosed. Feces and urine were passed. The animal became weak and could not stand. With a cannula a small amount of the intraperitoneal fluid was obtained. It was very dark and blood stained. The animal gradually recovered, and within an hour could walk. At 4.30 p. m. it was in fair condition, but still appeared sick. The abdomen was flaccid. Death occurred some time during the night.

*Necropsy.*—This was performed at 8.15, March 8, 1917. The animal had laid on the right side before and after death. There was a marked hemorrhagic edema of this side, which was 7.5 cm. thicker than the other side. The peritoneal cavity contained a small amount of dark-colored, blood-stained fluid. All visceral vessels were congested. The intestines were matted together with a thick, gelatinous hemorrhagic exudate. The liver was covered with this exudate. There was a double hydrothorax, there being more fluid in the right pleural cavity than in the left. The character of the fluid in the pleural cavity was the same as in the peritoneum. The mesentery and omentum were perforated with large holes, and in many areas only the blood-vessels of these structures remained. Except for cloudy swelling, all the other organs were grossly normal.

**EXPERIMENT 201-17.**—March 7, 1917, Dog B 837, a female brown and white mongrel, weighing 9.1 kg. Through a small stab wound, made under local anesthesia and sterile conditions, 400 gm. of Dakin's solution were passed into the abdominal cavity. The animal evidenced considerable irritation, vomited and struggled, but in general the condition remained good. The peritoneal fluid became dark and blood stained. The animal was very restless and died during the night.

*Necropsy.*—This was performed at 8.30 a. m., March 8, 1917. The peritoneal cavity and both pleural cavities contained a dark, bloody fluid. The intestines were covered with a thick hemoplastic exudate. All visceral vessels were congested. Omentum and mesentery were perforated in many places.

**EXPERIMENT 212-17.**—March 9, 1917, Dog B 844, a male black and white terrier, weighing 7.7 kg. The animal was etherized and the apparatus arranged to record carotid blood-pressure. The normal blood-pressure was 110 mm. Hg. Three hundred c.c. of Dakin's solution, temperature 35 C., were passed into the peritoneal cavity. Respiration was inhibited for about fifteen seconds. The blood-pressure increased slightly at first and then gradually decreased. After a few minutes 200 c.c. more of the solution were passed into the peritoneal cavity. The fluid which was allowed to flow back from the injecting tube was dark and

blood stained. The blood-pressure gradually decreased, and when it was 30 mm. the animal was bled to death.

*Necropsy.*—The fluid in the peritoneal cavity was blood stained and very dark. The visceral vessels were greatly congested. The mesentery and omentum were entirely gone except around the large blood-vessels.

EXPERIMENT 253-17.—March 11, 1917, Dog B 410, a male brown mongrel, weighing 8.3 kg. The animal was etherized and the apparatus arranged to record carotid blood-pressure. The normal blood-pressure

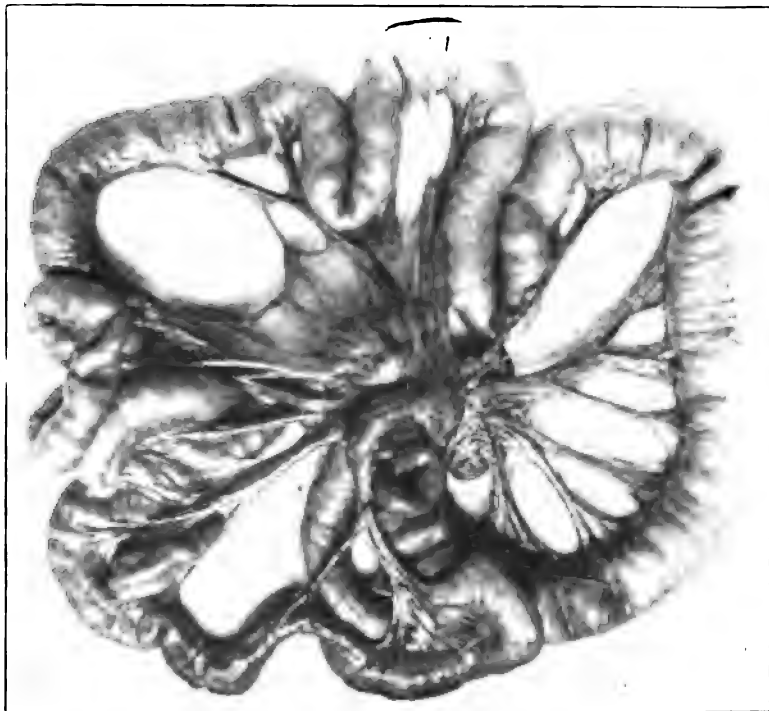


Fig. 442 (Experiment 212-17).—Intestine and mesentery after an intraperitoneal injection of Dakin's solution.

was 106 mm. Hg. Three hundred c.c. of Dakin's solution, temperature 37 C., were passed into the peritoneal cavity. The blood-pressure immediately decreased to 80 and then gradually decreased until thirty-five minutes after the administration of the solution, when it was 40. The animal bled to death.

*Necropsy.*—The findings were the same as recorded in the preceding experiment (Fig. 441).

EXPERIMENT 264-17.—March 20, 1917, Dog B 884, a male tan and white bulldog, weighing 12.7 kg. The animal showed the initial symp-

toms of distemper. At 10 A. M. 10 c.c. of Dakin's solution were injected intraperitoneally. The animal seemed to suffer severe pain. The injection was repeated every hour until 7 P. M., making a total of 100 c.c. of the solution injected. The dog seemed to suffer pain after each injection, although not nearly so much after the fourth injection. It vomited repeatedly after the last injections, but soon recovered from the effects of the solution, and was practically normal the next day. It died several days later. It is impossible to say what parts the distemper and the solution played in producing death.

*Necropsy.*—Slight lesions were found in the animal, as were noted in the preceding experiments, but the part they played in causing the animal's death could not be determined.

**EXPERIMENT 280-17.**—March 22, 1917, Dog B 895, a male brindle and white bulldog, weighing 14.6 kg. Ten c.c. of Dakin's solution were injected intraperitoneally every hour, beginning at 9 A. M. and continuing until 80 c.c. had been injected. The first injection caused considerable pain; later ones produced vomiting. The animal recovered from the injection, but developed a bad case of distemper and died twelve days later.

*Necropsy.*—Death was in all probability due to distemper, but undoubtedly the solution caused lesions as follows: (1) Perforation of the omentum and mesentery, and (2) edema and inflammation of the parietal peritoneum, especially in the dorsal region.

**EXPERIMENT 296-17.**—March 27, 1917, Dog B 783, a male brindle and white bulldog, weighing 8.5 kg. Twenty c.c. of Dakin's solution were injected into the right pleural cavity. No noticeable effect was produced in the animal. Ten c.c. of water, temperature 14 C., were injected into the peritoneal cavity; no effect was produced. Five c.c. of Dakin's solution were injected into the peritoneal cavity. The animal gave evidence of suffering intense pain, became restless, vomited, etc. With repeated doses, a total of 100 c.c. of Dakin's solution were injected into the external jugular vein. No effects were observed. The animal remained in good health.

**EXPERIMENT 303-17.**—March 28, 1917, Dog B 912, a male black and brown mongrel, weighing 4 kg. Twenty c.c. of Dakin's solution were injected into the pleural cavity. The animal moved during the injection and the tissues were infiltrated slightly. The animal seemed to be somewhat irritated, but soon recovered. One hour later 20 c.c. of water, temperature 14 C., were injected intraperitoneally. The animal showed no effect of either injection, and remained in good health.

**EXPERIMENT 304-17.**—March 28, 1917, Dog B 913, a male black and white terrier, weighing 6 kg. Twenty-five c.c. of Dakin's solution were injected into the peritoneal cavity at 9 25 A. M. There was immediate evidence of intense pain; the respiration and the heart were in-

hibited; the mucous membranes became pale, and the animal could not stand for several minutes. There was partial recovery one-half hour after the injection, when 25 c.c. more were injected intraperitoneally, with the same result. The animal also vomited.

At 4.30 P. M. the abdominal cavity was explored under sterile conditions. There were about 220 c.c. of slightly blood-tinged fluid in the cavity. The omentum and mesentery had disappeared in many areas, leaving only the large blood-vessels. The gastro-intestinal tract was markedly hyperemic, and there were many areas of edema of the posterior wall of the peritoneal cavity. The animal died two days later.

*Necropsy.*—Nothing of additional value was noted.

EXPERIMENT 319-17.—April 2, 1917, Dog B 803, a male black and white terrier, weighing 9.5 kg. At 9.15 A. M., 30 c.c. of Dakin's solution were injected into the external jugular vein. The animal did not show any effects of the injection, which was repeated every half-hour until 180 c.c. had been injected. After 150 c.c. had been injected there seemed to be a tendency of the vein to bleed after the withdrawal of the needle. Blood taken immediately after the injection of the last amount did not clot, but was laked with an unusual amount of plasma. Blood taken one hour later (12 m.) also failed to clot; but that taken at 5 P. M. formed a solid clot. The animal never showed any effect of the injection, and remained in good health until Dec. 7, 1917, when it was killed in another experiment. No change referable to the injection of the solution could be found.

#### REFERENCES

1. It should be emphasized that no conclusions are drawn either in regard to the use of Dakin's solution or the employment of the Carrel-Dakin method of wound treatment.
2. Carrel, Alexis, and Dehelly, D.: The treatment of infected wounds. New York, Hoeber, 1917, p. 32.



## PROBLEMS OF INFECTION\*

C. H. MAYO

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The chemistry of the world's activities is developed through the functional activity and protoplasm of the cell. The first forms of life, unicellular organisms, are lawless in their growth, multiplying without limit as food and environment are secured, either living together, or the stronger destroying the weaker. The common type of microbe lives on the weaker animal, on the plant, and even on inorganic life, completing its existence from lack of food or the resistance of the host; it then dries into spore form to again spring into action under suitable conditions. The lawless existence, naturally, in unicellular organisms is in marked contrast to orderly multicellular life. When the multicellular organisms appeared, true death entered the world. Under necessary control of growth and function, through community existence, they became the prey of the unicellular organism. We should not complain of the adverse action of a few of these organisms, because through cell action occurs the evolution of the world, and the ill effects of certain germs under abnormal and usually preventable conditions may be far outweighed by the other factors of their existence.

If the countless numbers of unicellular organisms are considered, many so small as to require the highest power of the microscope, and many of whose existence we know and have failed as yet to identify, it will be found that few in proportion to the total number are destroying agents. The greater part of the disease germs will be under the control of man's intelligence, if he has the power to enforce the preventive measures known to the world today. It is through such measures applied in earlier years of life that during the last thirty years the life of man has been lengthened appreciably. The microbes causing disease in man eventually bring about a period of his life in which sudden death occurs from affections of the heart, brain and kidneys, between the ages of fifty-two and sixty-two, as we have in no way changed middle age or

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advanced many more persons into old age. Death which is not accidental is due to the effects of the action of microbes, a result that may be acute and sudden or chronic and slow in its termination.

The contagious character of various diseases has been appreciated for untold ages, and it has been known that certain of these brought about some change in the individual which rendered him immune to a second attack of the disease. The first disease for which a vaccine was developed was that of smallpox, and, while it was used in China and India long ago, it was first used in Europe in Belgrade, and was given to the English-speaking people by the discoveries of Jenner.

A study of the blood in disease, as varying from its condition in health, and the action of its cells in developing antibodies capable of transmission, has been of wonderful value to mankind, since through this study acute diseases that have an immunity are reduced in morbidity and mortality by increasing the resistance of the patient, as in tetany, typhoid, paratyphoid, typhus, etc. Many of the diseases that formerly decimated mankind have been almost driven from the earth.

It is because of this wider knowledge of medicine that it has been possible to continue the present war without the destruction of the enormous armies by diseases which, if carried to them, would long since have brought the war to an unsatisfactory termination.

We find, then, that there is developed in the blood-stream in acute diseases and fevers an immunizing agent. On the other hand, with certain diseases there is in some place in the body small foci of bacteria continually maintained, developing not an immunity but an anaphylactic reaction, breaking down, instead of elevating, the resistance of the patient against the germ, by the constant supply of microbes or microbe toxin. Such persons are subject to recurring colds on the slightest provocation, recurring neuralgias, recurring myositis, muscular rheumatism, lumbago, etc. It has been enough in the past for the patient to say he is subject to such trouble, and for the doctor to make local applications and allow time to complete the cycle of improvement until, from any cause, lowered body resistance again renders the liability to an attack—and any part once affected by microbes becomes more liable to repeated attacks.

We have also protein poisoning. Many persons are unable to eat various grains or berries, milk, fish, etc., which cause them to develop asthma or chronic diseases of the respiratory tract or of the mucous membrane or skin, shown by local swelling, diarrheas, or eczema.

There are but few places in the body in which man quite regularly

carries bacteria; they are always in the mouth, often in the tonsil, and about the teeth in pyorrheas, alveolar abscesses, and buried crypts of tonsils. All tonsils capable of reacting to infection are of good size, 3 or 4 on the scale of 4, and are usually not the cause of chronic disease, but of strictly local involvement, and, when inflamed temporarily, develop systemic disturbances. A decision as to the real condition is most difficult for many physicians who have but recently come to a knowledge of the danger of a focus in these cases, not realizing that the blood-stream is the carrier of the infection. In such cases the localizing trouble in the sciatic nerve or in the joint did not begin there, but arose from the existence of bacteria in a minute pocket, and if that pocket is under tension, the disease is essentially chronic and recurring. The physician examines the throat and says the tonsils are not inflamed or that they are graded 1 or 2 in size and cannot be the source of the trouble. We must learn that the dangerous tonsil, as a carrier of disease, is the one that is classified 1 or 2, without any effects of local inflammation on its surface. The teeth through disease are often local foci of infection, and the x-ray has been of inestimable value in determining the presence of alveolar abscesses, absorbed roots, or absorbed bone about the roots. The findings are striking, when positive, but many such pockets do not show in an apparently good x-ray picture. The dangerous tooth is a crowned tooth, and if it is necessary from the seriousness of chronic, recurring diseases which affect the heart, as a myocarditis, the kidneys, joints, or nerves, then small tonsils must be removed, and teeth most carefully inspected, rayed and, when diseased, extracted on the basis of symptoms, should they be of major importance. Endarteritis and overgrowth of bone about the joints, including the hip and spinal vertebra, are also associated with minor types of bacteria, which are probably in pockets, or in open surface infections not under tension. Are they the cause of such infection or do they find here a home? We have far less fear of bacteria where nature holds them loosely; the dangerous ones are usually under tension and in small areas, although we must now come to the acceptance of the fact that the blood in apparently healthy persons often contains microbes.

In almost every conceivable place in our bodies, with almost no evidence of it, are living and growing the ameba, the syphilitic spirochete, the hookworm, and other germs too numerous to mention, and often apparently doing no more harm temporarily than trout in spring water. In many of us a little blood drawn and time given for growth will show

some kind of microbe to be present. We have wandering leukocytes with almost the power of animals to leave the blood-stream and forage for material dangerous to life, and then return to the circulation. The stomach does not destroy all the bacteria taken into it: some may pass into the blood by the chyle duct and probably more commonly enter the blood-stream by way of the portal circulation, when they are destroyed in the liver. No matter how well our food is prepared the germs in the mouth are carried on into the stomach, and after all food has left it, there are numerous bacteria living in the gastric juice in the majority of persons. The dangerous varieties of bacteria are those of the acid type, while the alkaline type are nuisances.

Next in importance to the microbe, from a biologic standpoint, is their environment in the chemical fluids of local areas. This is similar to the results obtained from seeds planted or blown on different soils. They may be planted to no purpose on the wrong soil, and they may be blown everywhere to take growth to advantage in proper environment. Bacteria carried throughout the body by the circulation are able to take up local growth only when carried to that area. This accounts for the specificity of bacteria in their location causing acute and self-limited diseases, or chronic recurring or relapsing diseases. The acidity, the oxygen tension, and the condition of the general health, or local injury, may all be factors. Some forms will grow only in a certain place, as poliomyelitis in the fluid of the brain and spinal cord, others in the sheath of nerves, the first causing acute conditions, self-limited, and the latter, recurring neuritis. Thus we have rheumatism, appendicitis, gall-bladder inflammation, ulcers of the stomach, and valvular diseases of the heart; in fact, nearly all the local and general diseases of which we have knowledge are in this manner produced, yet often the foci cannot be found. The question is, can a temporary focus develop a condition which is self-contained or does the chyle duct carry from the intestine?

The factors of safety are largely within the control of man in preventing the diseases, and in the transference of immunizing resistant bodies, such as have been developed for the cure and prevention of diphtheria, typhoid fever, smallpox, poliomyelitis, and many others.

Diseases of middle life are increasing. They are microbic, of a chronic, recurring character, and are carried into the blood-stream from a few foci, the mouth being the greatest danger. A crowned tooth is not a "crown of glory" and may cover a multitude of germs. Modern dentistry is relieving the world of much of its misery by watchful care

of foci connected with the teeth, the trend of modern medicine and dentistry bringing the fields again closely together.

In prevention and treatment we may search for and destroy the local foci if found; we may raise the immunity of the individual by vaccination; we may use serum, blood transfusions, and drugs for the increase of leukocytes. We may treat locally chronic, recurring secondary inflammations, increasing hyperemia, by Bier's method; heat may be used, and injections of mild irritants, and, on the biochemical theory, increasing the alkalinity of body fluids and the fluids of local areas to change from alkaline to acid and from acid to alkaline, in order to develop environments opposite that in which the bacteria are thriving.

Suppuration, unexpectedly appearing in incisions, is usually from the inoculation of the wound with skin types of bacteria. To avoid this it is necessary to protect the skin field while suturing. The result of such infection is shown early by the temperature. Late infection of wounds is usually due to faulty closure—a dead space with blood-clot which becomes inoculated by bacteria, temporarily or chronically contaminating the patient's blood. This is accompanied by little or no rise of temperature. A rise of temperature indicates that the infection was caused from without, the patient being unused to it.

Problems of infection, prevention, and treatment are being developed by the war. If a wound can be cleansed and the ragged borders excised within a matter of hours, primary suture with healing is a frequent result and prevents infection. This is not possible in a large percentage of cases because of necessary delay leading to much suppuration; thus more attention has been paid to overcoming suppuration and rendering the wound sterile for secondary closure. The results of the Carrel-Dakin method and of the dichloramin-T, especially the modified form, have been most encouraging when used in conjunction with the greater care of the wound.

The frequent testing of the secretion for microbes has been of great benefit, but probably the greatest gain has come from the frequent inspection and the personal supervision of the wound, permitting the intelligent use of antiseptics, wound stimulants, and antibodies.

## THE CANCER PROBLEM\*

C. H. MAYO

Through the study of comparative anatomy and embryology the anomalies of life have only recently become easier of explanation. It is shown that each life higher in the scale of evolution is subject to anomalies such as would be normal to some life lower in the scale. Certain additional forms accompany the changes from invertebrate to vertebrate. Within these two groups may be found the explanation for most of the anomalies, the cause in some being a chemical one—a change in the salts of the amniotic fluid, or of the solution in which the egg is developed. Is it not possible that the cancer problem may in time be worked out in many or all its details on the basis of primitive life? In truth, we advance far by the harmonious assembling of facts made known by many investigators.

Unicellular life of both animal and plant type divides the cell, and with it the cell intelligence for type and habits. We find that microbes may be changed from one to another of the same species by change in the oxygen tension, showing that variations of these organisms may occur with but little change from natural conditions. The polar bodies, centrosomes and chromosomes, do not occur in the unicellular organisms as found in the cells of multicellular organisms, and while unicellular growth is parasitic, increasing as long as food can be obtained and environment permits, in multicellular life each cell must be controlled for community existence and harmony of work, and the controlling agents are probably the chromosomes and centrosomes. The centrosome represents the dynamic power as suggested by Wilson. Cancer is probably created by the division of one cell failing to carry with it the centrosome, the next division of the incomplete half leaves it without control as a unicellular type of life, capable of lawless growth more or less true to type but without a controlling brain. In reversion of type the cell becomes parasitic in existence, creating nests of cells, fungating

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growth, ulceration and degeneration of connective tissue according to the location, tissue, and blood supply and reaction to irritation, and primarily changing the local field into a slightly acid one as an environment suitable for its growth. Ultimately this fluid permeates the body, a curious cancer cachexia occurs, and with it there may be metastases, later becoming manifest by growth at any point where cells may be carried. Before this it occurs in adjacent local lymph-glands permeated by the fluid, and cancer grows freely in them. It is this need for proper chemical fluid environment that explains why cancer cannot be transmitted into higher types of life, but can be transmitted in the lower. This explains the metastases occurring in cachexia, the whole body being in an acceptable fluid state, and in this state local operation seldom cures.

We might here consider why wounds heal and why cells repair and restore normal wear and tear. Ross has showed that leukocytes and lymphocytes and, to a less degree epithelium, may be caused to divide by heat, alkalies, dyes, and kreatin, also by putrefactive tissue and cell destruction, acting as its own stimulant. While irregular growths (anomalies) are increased by excess of salts, we believe acids are in excess in local areas of lawless growth.

Jacques Loeb has caused the unfertilized ova of sea urchins to develop by placing the eggs in a slightly acidulated sea water for a brief period and then into normal sea water for development.

Cancer continues to be one of the greatest of modern scourges. The disease apparently is on the increase, especially among the more highly civilized races. It may possibly be more prevalent than is suspected among lower types of the human race, because of lack of examination and investigation, as has been shown to be the case in cancer of animals, such as water buffalo, dogs, chickens, and mice and the lower types of life. In this connection Erwin Smith's work on cancer in plant life is of great interest. He has shown many plant tumors as being due to bacteria and insect irritation, and he has been able to reproduce and transplant certain tumors which compare in malignancy with those of animal cells. He shows drouth to be a stimulus to reproductive buds.

In cancer there is a local lawless cell growth. There must be, then, either a local cell fertilizing agent or a local loss of control over cell growth, and the study becomes one of the individual cell, the actions of which are best observed in early cell life. After maturity is reached there are few structures capable of cell growth, yet the thyroid, a dynamic

organ controlling energy output, is subject to hyperplasia, and the liver, a most necessary organ, is subject to regenerative growth. Primary cancer is relatively low in both organs.

Discussion, investigation, and discovery have been the means of controlling other great life-destroying diseases and have been most helpful in the control of cancer. Statistics show a marvelous improvement in the control and care of tuberculosis and of pneumonia, while cancer, apoplexy, nephritis, and diseases of the heart have all been increasing. The greatest advance, however, in our knowledge of disease has come from a study of the individual cell. MacCarty's investigations tend to show that the disease begins in the waiting or immature repair cells, which replace the active or protective epithelium, or the secreting cells, and not the mature cells. The necessity for overactivity of these resting cells by the stimulation of continued traumatism and the destruction of mature cells may be an important factor in the local origin of cancer. Thus rapid development and lack of control with migratory hyperplasia would place such cells within the cancer classification. The cell's intelligence for growth carries on progressive activity: the half of each active cell becomes the new cell, continuing its intelligence. Some investigators believe that a fertilizing agent of nucleated cells gains entrance to local areas through traumatism, and should a single cell become fertilized, cancer may develop. It is believed by some that the fertilizing agent of a cell is water-borne, and with some stretch of the imagination we bridge provoking difficulties of type, form, and location in a study of the cause of cancer. The biochemic theories of cell development are also advanced. The effect of cholesterol on the cell is being investigated. Educational propaganda has been of incalculable value in the prevention of cancer by early treatment, by the removal of benign tumors, and by the avoidance of irritation. It is probable that there are continually 200,000 people in this country suffering from the disease, and approximately 80,000 die each year of the disease.

While cancer may be found at any age, it does not commonly occur in persons under thirty-five years and it rarely occurs in persons under twenty years, when natural cell activity might be presumed to be a factor, and its disturbance would more readily develop uncontrolled growth. The resistant influence of youth may lie in the rapid reduction and restoration to normal of the acidity necessary to remove the ashes and waste developed in cell activity, and young cells have not exhausted the protoplasmic control bodies. In old age, with hardening of the tissues, it



is easier for a centrosome to partially or wholly fail in its material. If so, then the skin changes seen in the old, so-called precancerous conditions will occur, to become cancerous when one cell utterly fails in its control. Thus cancer would originate in one cell reverting to primitive life. The chemical change is naturally much slower in degenerating tissue or in the normal degeneration of advancing age.

In considering this chemical theory of cancer as influencing vicious cell growth, it is noted that of the cancers affecting man, 38 per cent in men and 22 per cent in women are found in the stomach where acidity is constant and high, as compared with other tissues. In ulcer, the gastric secretion is high in free acid. When cancer develops, combined acids increase and free acid diminishes or disappears, and the activity of pepsin is reduced or destroyed, regardless of the presence of combined acids. In accordance with this hypothesis peptic ulcer and cancer would occur but rarely in the non-acid achlorhydric stomach, since destructive growths and destructive bacteria are most harmful in the acid environment. The duodenum, which by right of continuity of tissue and close association, and opportunity for grafting from cancer of the stomach, is far more commonly affected by ulceration than is the stomach, but it is rarely affected by cancer which, nevertheless, may spread from the stomach into all other tissues and structures surrounding it and also at distant points in the abdomen. Ulcers occur in the stomach about one-third as frequently as in the first portion of the duodenum. A large percentage of gastric cancers give a history of preceding ulcer. Ulcer, then, is more common in the naturally alkaline duodenum, which is periodically bathed with the acids from the stomach. The neutralizing process occurs in the first portion of the duodenum. Ulcer or cancer is very rare in the duodenum below the first two or three inches, although cancer occasionally occurs in this organ by penetrating through a duct. Cancer occurs but twice in the whole length of the alkaline small intestine to ninety-eight times in the large bowel. The colon is frequently affected by cancer because here again there is acidity, and 75 per cent of cancers are located in the fixed and tissue-surrounded portion of the colon, which retains the dry and harder contents as a traumatic agent. The same statement may be made concerning the development of cancer in other acid fields, either normal or degenerative, that is, the urinary bladder, the cervix, and the mouth. The mammary gland, the uterus, and the prostate are subject to carcinoma, being tissues in which degeneration is a normal process and having but a limited period of functional activity.

Ulceration, under proper conditions, may permit cancer to develop. The ulcerative process itself is usually of bacterial origin, and the bacteria are carried by the circulation, local conditions of infection being developed through capillary infarctions. It is very probable that the essential factor in the development of carcinoma is a derangement inside of the single cell in an acid field, and that the single cell carried through the lymphatics or into the circulation is the cause of metastasis. In the peritoneum and on the surface grafting is common, and it is occasionally seen in epithelial and mucous surfaces.

It is evident that cancer is on the increase among the more highly civilized people; the enormous percentage occurring in the stomach would indicate that this organ received the greatest abuse. Many factors concerned with the higher civilized existence probably tend to the increase of cancer and should be a subject for study.

We have, then, in cancer a cell with lost control, destroying its community existence and reverting back to primitive life. It has a natural acid environment or an acquired one incident to local degeneration which may be normal, as in the stomach, or incident to normal degeneration, as in the breast and uterus, or the degeneration of age.

The part played by chronic traumatism or irritation in the development of cancer is positive and definite to a degree. The danger of cancer is increased by all irritation or traumatism which demands a continued cell repair, and it is in proportion to that demand. Ultimately exhaustion of cell control bodies occurs, modified by age limitations and chemical surroundings. Such areas offer an increasing opportunity for the half of a dividing cell to revert to the unicellular outlaw type of life and to become parasitic and cancerous.

If the cells are involved, they must be of the immature or waiting type, and further progress in the study of cancer can come only through a study of the individual cell of the multicellular and unicellular organisms, in order to select more definitely the one or more bodies which may be involved in the control of its protoplasm.

#### TREATMENT

Removal by any method is effective, if early, whether by knife, paste, cautery, rays, or radium. Removal of the local growth is not effective if the glands are involved, more extensive dissection being required in addition to gland removal.

The effect of rays may be to lower the permanency of the control bodies of the cell; thus prolonged x-ray treatment without protective shields, for certain types of rays, adds a factor of danger in the production of cancer.

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# TETANUS AND THE WAR—A REVIEW OF THE LITERATURE\*

A. H. SANFORD

Tetanus is the "black beast" that lurks in the shadows for the convalescent wounded soldier. The maelstrom of the battlefield may be safely passed; the soldier rejoices in having received only a slight shell-wound, and is invalided home for a few weeks; but terrible indeed may be the end if that bit of shell has carried with it the spores of the anaërobic tetanus bacillus. As all statistics of other wars have been surpassed in the present conflict, it is not surprising that there has been an enormous number of cases of tetanus reported. It is a matter of comment, however, that in 1914 especially, the ratio of tetanus infections to the total number of wounded far exceeded that found in previous records.

The literature on tetanus as it relates to the war during the past three years has been voluminous, as evidenced by a glance at the bibliography and it has not been possible in this paper to review it completely. To correlate these statistics will be more properly a task for the historian of the future. Statistics at this time are not popular, nor are reports any too authentic from the various belligerent nations. There are some articles, however, that stand out as adding a great deal of information to our previous knowledge of tetanus. Robertson, of the University of Minnesota, in reporting his studies on tetanus, has thoroughly reviewed the early literature, and has emphasized the necessity of applying our knowledge of prophylaxis to war surgery. Our own Medical Corps especially may profit by the official reports of the surgeon-generals of the British forces. Sir David Bruce, Surgeon-General, Chairman of the War Office Committee for the study of tetanus, has made an analysis of the cases of tetanus treated in home military hospitals that is especially valuable. His last report this year (September, 1917) makes public the statistics of these cases to the end of 1916.

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The incidence of tetanus to the total number of wounded in the British forces was 16 per 1000 in September, 1914; 32 per 1000 in October, 1914. Sept. 8, 1914, the telegram arrived at the front, "Earl Kitchener desires information as to whether antitetanus inoculations are being practised for the wounded and whether, if not carried out in the field units, they are carried out in communication units. He wishes all to be impressed with this." In November, 1914, the ratio fell to 2 per 1000, and this has been the ratio with very slight fluctuations since then. This fall is undoubtedly due to the introduction of prophylactic injections of antitetanic serum for all the wounded. We might compare with these figures the early reports of the incidence of tetanus among the Germans of 6.6 per 1000 at one base (report of Madelung). A report by Kümmell places the incidence among the German wounded at the same unusually high percentage, 6 to 6.5 per 1000. The data from other sources are not quite so reliable. Italy does not seem to have so much tetanus although there are many references to individual groups of cases. The French figures are not complete. Courteaud reports recently that since the beginning of the war there have been 58 cases of tetanus among 60,000 wounded appearing at Cherbourg. This is a surprisingly low number, as it is less than 1 per 1000. However, the same article states that in the region of Cherbourg tetanophobia is rampant among soldiers, sailors, and civilians and they come to the hospital for prophylactic injections for the least scratch. In fact the author pleads discrimination lest the available supply of serum be exhausted in useless administration.

Bazy, in a report in 1914, states that when prophylaxis was practised by every wounded man the incidence was 4.18 per 1000 and when the injections were made only in suspicious cases the incidence was 12.79 per 1000. Also that in a batch of 200 wounded soldiers 100 received prophylactic injections, and there was one case of tetanus. In the second 100, because of no available serum, there were 18 cases of tetanus. It is evident then that at times at least this has been a big factor to deal with in the French wounded. The reason for the overwhelming incidence of tetanus in the present war can be attributed doubtless to what has often been referred to as the tetaniferous fields of France and of Flanders.

In this connection it is interesting to review the statistics of some of the wars of a generation ago, long before the discovery of the tetanus bacillus by Kitasato in 1889, and the prophylactic antitetanic serum of von Behring. In the Crimean war the English report 12,094 wounded with only 9 cases of tetanus, or 1.5 per 1000. The Medical and Sur-

gical History of the War of the Rebellion gives a total of 246,172 injuries among the soldiers of the United States Army, with 505 cases of tetanus, or slightly more than 2 per 1000. It is stated that in the Franco-Prussian War there were 350 cases among 95,000 wounded, an incidence of 3.5, and in the Russo-Turkish war (1877-1878), 66 cases among 51,700 wounded—the very low ratio of only 1.2 per 1000. It would seem then that at the present time, following out all of the measures that modern science and strict military discipline can impose, the very best that the armies of the world can do is to keep the incidence of tetanus in their wounded to about the ratio that has been reported in past conflicts.

A discussion of the character of the disease may not add anything to our knowledge of the subject. However, it is of interest to note the many types that have been reported.

It must always be remembered that we are dealing with a local infection, with a virulent toxin making its way to the central nervous system by way of the perineural lymphatics. The character of the disease is affected by the extent of the injuries, many wounds making many foci of infection, and also by the treatment of the wound at the first dressing station.

The classic picture is that of so-called "tetanus descendens," common to man and horse. In this condition trismus, or "lockjaw," is the first symptom. The spasmodic contractions then occur in the various parts of the body, appearing in their sequence from above downward. The opposite of this condition is "tetanus ascendens," which is first localized to the wounded limb, and then extending upward it becomes general.

There are many reports of localized tetanus. Usually the patient complains of pain before the spasms and board-like rigidity of the muscles are apparent. This should always be thought of if the patient is complaining of "rheumatism" in the wounded limb. For years it has been thought that the lower limbs are the more common locations for wounds from which tetanus develops. This is confirmed apparently by war statistics. McArdle also mentions that the thumb is a rather common location for wounds that result in tetanus, the lymphatics of the median nerve quickly carrying the toxin to nerve-centers. Wounds about the head may harbor the germs of this disease, but it is unusual for wounds of the chest or abdomen to be the focus of tetanus.

One rather common type of disease is delayed tetanus. Usually in

such cases at least one prophylactic dose has been given at the front. This undoubtedly modifies the type so that instead of the acute, flamboyant, quickly fatal tetanus, there is a period of latency. Miller, Inspector of Tetanus at Edinburgh, reports a typical case. The man was wounded Oct. 22, 1916, at the Somme, and received prophylactic treatment on that day and also October 30. November 22 there was a slight rigidity of the left arm. December 15 he returned to duty. Jan. 5, 1917, he complained of a pain in the head. January 9 he was sent to the hospital, where two days later (January 11) a definite trismus was noticed. In spite of active treatment with antitetanic serum the patient died January 13, or eighty-three days after he was wounded.

Barling reports three cases of delayed tetanus, one occurring fifty-one days, another fifty-three days, after injury; both of these patients recovered. The third patient developed tetanus forty days after injury and died finally of gas gangrene, which set in seventy-three days after the injury and forty-two days after the healing of the wound. Dean, in his report of 25 cases, states that in 10 cases the incubation period was more than fifty days, the longest time of onset being one hundred twenty-seven days after the patient was wounded, but thirty-one days after an operation. Another case occurred one hundred two days after the patient was wounded, and one hundred days after an operation.

Two of Foster's three cases of delayed tetanus are of special interest. The third case developed after an incubation period of eighty-six days. Cases 1 and 2 were patients whose wounded arms were injured by falls during convalescence. The first patient developed tetanus one hundred forty-six days after receiving the wound, and the second one hundred six days after the initial injury. All three of these patients recovered. In this connection there is an interesting report in the German literature by Doberer of an Italian prisoner of war who developed tetanus one hundred twenty-eight days after injury, from which he recovered. A month later scraps of shell were removed and tetanus again flared up for five days. Mice injected at this time with material from the wound developed tetanus. The patient recovered, so that the dictum of Coombe, in his article on this subject to "let sleeping dogs lie," might be well heeded. He suggests that there should be great care in any interference with a granulating wound in war-surgery.

Still another case history reported by Westwater states that forty-two days after the first attack his patient developed a second attack from which he died. Constant vigilance seems to be necessary to avoid

late or recurrent tetanus in instances in which the disease might be expected to occur.

Both Surgeon-Generals Makins and Bruce report the occurrence of tetanus developing as a complication of trench foot. The latter states that in the last few weeks of 1916 there were fifteen cases developing after "trench foot." He emphasizes the importance of giving weekly prophylactic injections of serum in this condition.

There would seem to be little difficulty in diagnosing tetanus if one keeps in mind the various types that may occur. Pribram states, however, that it might be necessary, as it was in two of his cases, to differentiate tetany from tetanus. The presence of irritability of the facial nerve, of a strained position of the hand, and of isolated adductor spasms are mentioned as diagnostic points in tetany.

The prognosis in tetanus depends now as ever on the incubation period, on the rapidity of onset, and on the duration of the disease. Modern experience makes no change in the old statement of Kanthack that "fatality is in direct proportion to rapidity of onset, and inversely proportional to the duration of the disease." In fact Hippocrates stated that "such persons as are seized with tetanus die within four days, or if they pass these they recover."

As has been mentioned, prophylactic injections undoubtedly have much to do with the prognosis. The late tetanus that occurs after antitetanic serum has been administered at the time of the first dressing has usually proved to be less fatal. Sir David Bruce says: "The incidence of tetanus among wounded men falls sharply on the introduction of prophylactic injections of antitoxin, and it is much to be desired that the primary injection be followed up by secondary and further prophylactic doses as long as the wound remains suspicious."

We in the United States are not inexperienced with tetanus. The *Journal of the American Medical Association* each year since 1903 has gathered reports of "Fourth of July tetanus," and the lay press has done much to educate the public as to the danger that lurks in the apparently simple powder-burn. In the years 1903-1915 inclusive there were 1119 cases of tetanus resulting from accidents arising in the celebration of Independence Day, and 991 persons died. There is, however, something very encouraging in these amazing statistics, that is, the years have shown constant and remarkable improvement. In 1903 there were 415 cases and 406 deaths; in 1912, 7 cases and 6 deaths; in 1913, 4 cases and 3 deaths; in 1914, 3 cases and 3 deaths, and in 1915, only 1 case. Since



then there have been no cases. Prophylactic injections must have played a great part in making this most satisfactory change, though the regulations in the large cities that make for "a sane Fourth" have made accidents rare instead of common.

The advice of the surgeon-generals with the British forces is to do very little locally in attempting to remove the infection after the first operation. If foreign bodies can be removed or amputations are necessary, precede such procedures with prophylactic injections.

Tizzoni showed experimentally that dressings in which antitetanic serum had been dried, when applied to wounded surfaces infected with tetanus, protected the animals from the disease. It has been suggested in the Italian literature that this be given clinical trial, but there are practically no statistical reports as to its efficacy.

As soon as symptoms of tetanus appear, treatment is carried on most strenuously, and with watchful care. In our civil war the treatment is frankly described as "empirical to the last degree." There are mentioned 28 different drugs that were administered by mouth, and 16 different sorts of local applications for the cure of tetanus. It is little wonder that the mortality was 89.3 per cent. Though in spite of our best efforts we may expect an incidence little better than in previous wars, still the methods of treatment now at our command are rational and hopeful.

Statistics regarding mortality vary. Sir George Makins, Surgeon-General, consulting surgeon to the British armies in France, has stated within the year that in spite of treatment the mortality is above 70 per cent of all cases treated. It must be remembered that these patients were severely wounded and could not be transported to England.

The reports of Sir David Bruce\* are more encouraging. From the home military hospitals there have been four different series reported: In 1914-15, 231 cases, 57.7 per cent mortality; in 1915-16, 195 cases, 49.2 per cent mortality; in August and October, 1916, 200 cases, 36.5 per cent mortality; October to December, 1916, 100 cases, 31 per cent mortality. He has hopes that the mortality may finally be reduced to 20 per cent. The incubation period tends to become longer, as only 12 of the last 100 cases occurred in less than ten days from injury. There were no deaths at all in 29 cases in which there was localized tetanus.

\* Sir David Bruce reports the cases from December, 1916, to March, 1917. In this period there were 100 cases treated in the home military hospitals, and the mortality was only 19 per cent. (*Lancet*, London, 1917, No. 25, ii, 925.)

Treatment is specific and symptomatic. Specific treatment consists in the administration of antitetanic serum. As prophylactic measures, 500 to 1000 U. S. A. units are injected subcutaneously, the first as soon as possible, and then at weekly intervals until the wounds heal. After symptoms develop the manner of administration and the dosage will be the subject of some unfortunate controversy. At the outset subcutaneous or intramuscular injections of several thousand units may neutralize the toxin. Leishman and Smallman insist that this is the best method for treating the disease throughout its course. They divide the dose and inject some into the muscles of the injured limb if feasible. Daily doses of 10,000 units are given for the first few days. Some authors have advocated injections into the main nerve-trunk if possible, especially when localized tetanus is the first sign. Though early reports advocated the intravenous administration of serum, this has been practically discarded as the results do not warrant the great risk of anaphylaxis that all patients run.

In the home military hospitals in England the method used uniformly is the intraspinal. Fluid is first withdrawn and as many units as can be safely given are introduced. An ordinary first injection is 3000 units, although by using the concentrated form, the globulins only, as much as 30,000 has been injected intrathecally. With this are combined intramuscular injections. Professor Sherrington conducted a series of experiments for the war office committee for the study of tetanus. Twelve infected monkeys were treated intramuscularly—all died; while of 18 monkeys treated intrathecally, 13 recovered. This would seem conclusive evidence of the advantage of introducing antitoxin directly into the spinal canal.

The symptomatic treatment of the disease is sedative and antispasmodic. The treatment of Meltzer and Auer with magnesium sulphate was advanced in this country several years ago, and has many advocates, especially in Germany. It consists of injecting concentrated solutions of magnesium sulphate which has a marked antispasmodic effect. If given subcutaneously, it is used in 25 per cent solution. Not more than 2 c.c. nor less than 1.2 c.c. per kilogram body weight is injected four times a day, the patient being lightly etherized. This is the advised routine method of administration. Occasionally the same dose may be injected deeply into the muscles of the thigh. Massage should be administered, and the etherization continued for twenty minutes following the injection. As an emergency measure magnesium sulphate may be

injected intravenously in isotonic solution (3 per cent) at the rate of 5 c.c. per minute. The spasm may be controlled for a longer time by intraspinal injection of 25 per cent solution, giving 1 c.c. per 10 kg. body weight. The dangers lie in the possibility of paralysis of respiration. When given intraspinally, the fluid may be drawn off from the canal if this catastrophe occurs. Meltzer also advises the use of his pharyngeal insufflation apparatus for the maintenance of artificial respiration. This method after a few trials has been practically abandoned in England. The same might be said regarding the Bacelli treatment with carbolic acid. This treatment, however, seems to meet with favor in Italy. Carbolic acid may be used in 1 per cent solution, injecting 40 c.c. up to 70 c.c. daily. The action is supposed to be both antitoxic and sedative. The reports in the literature are not very favorable. When this is the only method of treatment, the cases are uniformly fatal. When combined with serum treatment, recoveries are reported, but of course this nullifies any deductions as to the value derived from the phenol.

In conclusion, then, we may state in substance the summary with which Sir David Bruce closes nearly all of his reports. Prophylactic injections must be carried out persistently for all wounded and "trench foot" cases. The most hopeful cases are those of late or delayed tetanus. Reports are not conclusive regarding the effects of serum therapy. Treatment is outlined as follows: (a) Rest, sleep,<sup>1</sup> food; (b) surgery must be early—later on do not disturb the wounds; (c) administer large doses of antitoxin intrathecally and intramuscularly, or subcutaneously; and (d) in addition, if necessary, use the common sedatives, morphin, chloral, or chloretone.

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## MODIFICATIONS OF SOME CIVIL SURGICAL PRACTICES SUGGESTED BY THE SURGERY OF THE WAR\*

W. J. MAYO

At the time of the outbreak of the great war in the summer of 1914 military surgery did not differ in any important respect from civil surgery. Drainage of wounds was almost universally practised; suppuration was to be expected; and either primary or secondary amputations in extensive injuries of the extremities were the order of the day. Industrial surgery, however, was making a place for itself and, it might be said, has paved the way toward modern military surgery.

Civil surgery has largely to do with conditions brought about by disease in which there is a marked reduction in the vitality of the patient, and in which the patient cannot be depended upon to react promptly from gross surgical injuries. Civil practice has also been hedged about by certain surgical precepts, based in part upon tradition and in part upon fact, that have made the surgical profession conservative. War surgery soon demonstrated that the young, strong, well-nourished soldier has a power of resistance that is far beyond the average found in civil life, and that he not only can react but also does so in a way that had been assumed, from our previous surgical experience, to be impossible.

The first lesson to be drawn from war surgery is that measures which might be inappropriate in the old, the diseased, and the feeble, could safely be carried out in the young and strong, and that we had possibly underestimated the ability of even the former class of patients to make a better and safer recovery by the employment of less elaborate technic and by greater dependence upon their natural resistance.

A second lesson which the war has brought home to us is a clear differentiation between the contaminated and the infected wound. By contamination is meant the soiling of a wound with material which

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would certainly produce sepsis if left, but which, if removed promptly before infection actually takes place, will leave the wound in a condition for primary union, or, if in a border-line case, proper treatment with temporary packing will afford an opportunity for secondary suture, and recovery will be almost as prompt.

A retrospect of the surgery of the last twenty-five years shows a gradual diminution of the practice of drainage. With each successive year from the time when every wound was potentially infected and drainage was used constantly, to the beginning of the modern treatment of wounds in general, we have seen fewer indications for drainage. This has been true not only of contaminated and as yet uninfected wounds, but also of the treatment of late more or less sterilized infections as they exist in the pelvis, for example. The father of modern abdominal surgery was Lawson Tait, of England. He was to Europe what Joseph Price has been to America—both were men of strong character, great resolution, and surgical skill. Both of these men used drainage in almost all abdominal work. Slowly it was recognized that if acute infections within the pelvis were operated upon in the earlier stages there was a high death-rate, but if the patients could be tided over this phase and operated upon in the later stages, there was little danger, since the infecting organisms would have become too attenuated to do much mischief, and in the meantime protective antibodies would have developed. Drainage, therefore, was no longer the necessary adjunct to pelvic operations for the relief of sterilized infections that it had been in the past. Joseph Blake led in the avoidance of drainage in contaminated wounds of the abdomen operated upon early, such as those following perforations of abdominal viscera. It gradually became manifest that drainage had been overdone, that it was better thoroughly to cleanse and sterilize a contaminated wound, and, instead of following the old rule of “when in doubt, drain,” the new rule, “when in doubt, don’t drain,” was accepted. It was also learned that even when drainage was required a little strip of rubber tissue that would furnish an outlet for retained secretions was better than the ordinary drain. As I look back over an extended experience with drainage, I am impressed with the infrequency with which real drainage has followed in contaminated and not yet infected wounds, and with the fact that the secretions which were drained away in the first few hours after the introduction of a drain would have had great power for good and none for evil. Especially has the old practice of inserting drainage gauze, unless rolled

up in rubber tissue, become obsolete. Royster has put the query: "When does gauze fail to drain?" The answer is: "When it acts as a plug." Many a time I have carried a strip of gauze for a drain close to a damaged piece of bowel or in the vicinity of an intestinal suture to have a fistula form on its removal. It was years before I learned that the gauze, by removing the plastic lymph which should protect the damaged intestine, was the cause of the fistula, rather than that it had saved the patient's life by leading the intestinal contents to the surface.

Looked upon from the standpoint of abdominal surgery, therefore, in both civil and military practice, the drainage of contaminated wounds that can be reasonably cleansed is usually unnecessary and often harmful. The drain has merit in the few cases in which it is necessary to quarantine an infected area and to maintain a communication to the surface which will become canalized and enable the wound to heal from the bottom, or occasionally to act as a possible telltale for concealed hemorrhage.

A gauze pack to check venous and capillary hemorrhage may rarely be required in abdominal surgery. In using the pack under such conditions, twenty-four to forty-eight hours is quite sufficient, but if the end of the pack is left projecting from the abdominal wound, it will sometimes permit the entrance of bacteria into the deeper cavity and necessitate further drainage. For some years, in the occasional case, I have followed the practice of inserting a pack of even several yards of gauze, closing the abdomen completely, tying the abdominal sutures in double-bow knots, removing the perfectly aseptic pack at the end of twenty-four to forty-eight hours, and drawing the sutures again into place, closing the wound completely, and thus avoiding the annoying and sometimes dangerous pack infections. What has been said of wounds of the abdomen applies to wounds of the thorax, in which primary closure with repeated aspirations of pleural exudates or small drains, with the use of sufficient Carrel-Dakin solution injected into the contaminated thoracic cavity to keep the exudate in a fluid state so that it will readily flow out, have largely replaced the huge thoracic operations recently in vogue for infections. In wounds of the joints the same practice holds good: excision of the wound margins, closure by interrupted sutures, leaving a little space between them for any drainage to find its way out, and then instituting Willems' method of early active motion. I well remember when the plaster cast fixation of the sprained ankle or other joint led to prolonged and often permanent

joint adhesion disability—such fixation has now, fortunately, become obsolete—that of early motion having taken its place.

Largely due to the originality of the French, but now adopted by all the allied surgeons, debridement, that is, painstaking and careful excision of contaminated and damaged wound surfaces and removal of all foreign bodies, is now widely practised. If debridement is done early, the wound may be closed at once without drainage. More than 90 per cent of primary unions have followed such closure of wounds. If there is doubt about the thoroughness of the procedure, or as to whether the stage of contamination has passed on to that of infection, debridement is carried out and the wound is packed with plain or medicated gauze, often saturated with ether. This pack is removed at the end of from four to six days and a secondary closure made, a practice, especially when used in conjunction with the Carrel method of bacteria count, which has proved exceedingly safe and has given as high a percentage of early unions as primary closure. Debridement with primary or secondary suture is now used in the majority of wounds that were formerly drained and permitted to heal by the old slow process of infection and granulation and the formation of disabling scar tissue.

The third lesson to be drawn from war surgery concerns shock. How much we have heard about shock, yet how little we know of it! It is exceedingly rare in civil practice, but is occasionally seen in industrial accidents. It is largely associated with huge traumatisms and, at least as seen in the operating room, is due to a combination of blood loss and prolonged procedures which require gross and forceful manipulation. I have seen shock without blood loss, as in the case of a man whose legs were cut off by being run over by a locomotive. I have seen shock from traction and injury to the mesentery of the small intestine, but shock as I have generally observed it has been so closely associated with hemorrhage that I do not feel that it can be discussed adequately except in connection with actual or potential hemorrhage. The experimental work of Mann, of which I have had direct knowledge, serves only in my mind to strengthen this relationship, and I believe that we may set it down as a rule that shock is associated with hemorrhage or its equivalent. Out of the fog which surrounds the shock problem some light begins to appear. Archibald believes that in shock there is blood loss into the dilated capillaries of the tissues. Cannon accepts this theory and calls this form of tissue blood loss exemia. The relationship of acidosis to shock also appears to be better understood. The acidosis is

one of the results of the failure to oxygenate the tissues, a result, not the cause, of shock. The lactic acid developed in the asphyxiated tissues reduces the alkaline reserve. Possibly, bicarbonate of soda may help to relieve the acidosis. What is needed, however, is the restoration of the circulation and the maintenance of blood-pressure. Bissell has shown a peculiar connection between certain kinds of shock and fat embolism, on which further study is being made, and important results are to be expected. There has been some attempt to divide shock into primary shock, like an exaggerated fainting attack, and secondary, or true shock, which comes on later. The first is more properly termed temporary collapse and is not true shock. In typical shock the patient's skin is ashen-gray, possibly slightly congested, and is covered with a cold, wet transudate which is not like perspiration. The blood-pressure is well down under 100 and the pulse is feeble, rapid, and of very small volume. The patient shows diminished mentality, although he may be aroused to answer questions if spoken to rather sharply. The French make it a rule, not a law, not to operate if the blood-pressure is under 100 and the pulse-rate is over 110.

In pure hemorrhage the picture is very different. There are pallor and restlessness with great acuteness of mind. The patient may be perspiring, but, if so, it is a true perspiration and not transudate. In hemorrhage during operation the blood-pressure will be reduced, the pulse feeble, and the leukocytes relatively increased, the picture being quite different from that of shock. If we keep these two pictures in mind, we can sometimes estimate the part played by active hemorrhage in the development of shock in an individual case, remembering that the effect of effused blood in the abdomen and pleural cavities, aside from the effect of the loss of blood, is to add in some peculiar way to the existing shock.

The failure of experimental evidence to satisfy investigators and the failure of anything like an agreement as to the cause of even the most common features of shock, renders further comment on the problem at this time unnecessary. Unfortunately, shock is one of the most frequent causes of death following those formidable war injuries at the front, but, fortunately, there is much unanimity as to the treatment, which, generally speaking, is the same as that carried out in civil life before the war, with some features sharply accentuated: (1) Checking hemorrhage, stabilizing wounds and fixation of fractures; (2) morphin, dry heat, elevation of the foot of the litter, and, if the patient is thirsty,

hot drinks, tea with a little sugar, and bicarbonate of soda and glucose, best perhaps by the rectum; (3) most important in those cases in which hemorrhage has largely to do with the cause, transfusion of blood, or, if blood cannot be obtained, gum acacia solution. While blood transfusion has been used more or less since 1648, in the modern sense it is the product of that indefatigable experimenter and surgeon, Crile, whose remarkable work of ten years ago is appreciated more and more every day. For war purposes as well as in civil life, citrated blood which may be kept in cold storage for a considerable length of time, and which may readily be given by gravity, has proved the best method. The Moss-Brem type of estimation of the blood of the recipient and donor to prevent hemolysis is an easy and reliable method. In this connection the demonstration that Group IV blood does not cause hemolysis of any other blood emphasizes the fact that the chances of accidents in military surgery are still further reduced by having, if possible, Group IV blood in cold storage. Intravenous use of salt solution has proved so temporary in its effect as to have only moderate value. Leaking blood-vessels and capillaries, whether cause or effect, are one of the outstanding features of shock. Salt solution, therefore, does not stay in the vessels, but rapidly passes out and if given in large amounts still further clogs the asphyxiated tissues. This effect has been at least partly overcome by the use of gum acacia solution, as introduced and practised by British surgeons. A 6 per cent solution of gum arabic in salt solution can be sterilized and the resulting mucilage forms a colloid solution which has the proper viscosity to remain within the vessels unless, of course, there is a hopeless traumatic leak from one of the larger tubes. Gum acacia solution is given in the same amount and for the same indications as blood transfusion. Experimental and clinical evidence appears to demonstrate the remarkable efficacy of this simple method and that the acacia solution is quite harmless. This form of transfusion is especially adapted to front line work and, in conjunction with the application of heat, elevation of the foot of the litter, fixation of large fractures, and morphin, may enable a grossly injured man to reach the evacuation hospital in condition for a life-saving operation instead of as a dead man. In this work at the front lies a great lesson to the civil practitioner. In his medicine bag may be placed a half pound of gum acacia, a funnel, a rubber tube, and a needle; in every home may be found salt, water, fire, and a piece of flannel for a strainer, and he, too, depending only on his own resources, will be prepared to save life in cases of hemorrhage. If the shock is not

connected with blood loss, transfusion of blood, acacia solution, or salt solution has little value.

The fourth lesson to be applied from our knowledge of war surgery is that of anesthesia. I was once asked how to hold the audience in the Section on Surgery the last day of a general medical meeting. I suggested that the discussion of shock and anesthesia always occasions a free-for-all in which there may be a wide divergence of honest opinion and an equal opportunity for all to express their views. As I have talked with military surgeons from abroad, I have found the expected difference of opinion, especially as to just what anesthetic to use in case of shock. It is impossible to sum up these opinions, because the same facts are called upon to maintain the individual as well as the group opinion, whichever side may be taken. It is evident, however, that ether by the drop method has more than held its own as the anesthetic of war. The ether in the small can, which the trained nurse can carry in her pocket, produces sleep quickly, acts as a stimulant, and quiets rigidity. Ether may be said to be the anesthetic of choice for abdominal work and for handling gross injuries either at the front or at the base hospital. Primary ether may also be used for short operations and dressings, but for painful dressings, such as the removal of packs for secondary suture, done in the rear, and short operations at the base hospitals, where complete relaxation is not necessary, nitrous oxid and oxygen anesthesia has a great deal to recommend it. It is manifestly impossible to take the big gas and oxygen tanks up to the front line and a combination of ether, nitrous oxid, and oxygen usually means a camouflage in which ether plays the chief rôle and the nitrous oxid and oxygen get the credit. Local anesthesia does not play a large part in acute military surgery, but in reconstructive work at the base hospitals it has a wide field of usefulness. The occasional operator in civil life who does not have a skilled anesthetist should learn to use local anesthetics. He will be surprised to what an extent this will enable him, without trained help, satisfactorily to perform operations. Spinal anesthesia has been abandoned, but we must remember that the spinal cord does not enter the lumbar vertebral space, and therefore injections of local anesthetic into the lumbar spinal canal amount to a nerve blocking. It is possible that spinal anesthesia may yet play an important part in war surgery.

In conclusion, I wish to express my thanks to Colonel Charles H. Peck for certain facts referred to in this paper that were contributed from his personal experience at the front.



## THE RELATION OF LABORATORIES TO HOSPITALS\*

WM. CARPENTER MACCARTY

The art and science of medicine have arisen out of the natural reactions of all living matter to its antagonists in its environment.

The object of such reactions has been one of protection of life from immediate or gradual extinction. Such protection—which seems to be the dominant immediate motive of life—has been both individualistic and communistic in that the life-history of the whole of mankind is dependent upon that of the individual.

These fundamental generalizations of biologic facts affect us as human beings and manifest themselves in our efforts to cure, ameliorate, and prevent the ills which have burdened man since, and probably before, the beginning of all written records of his earthly activities.

From the simplest reactions, which are common even among the lowest animals, man has established, with his increasing methods of obtaining, correlating, and utilizing knowledge, a complex and essential branch of activity which to-day is being realized to be the basis of all human earthly progress.

The realization of this fact is the reason for the splendid efforts which you as individuals and an association are making to improve the methods by which mankind will be happier and more progressive.

By the term laboratory, of which I am to speak, is meant “a room, building, or workshop especially fitted with suitable apparatus for conducting investigations in any department of science or art.”

This definition correctly means that the whole hospital is a laboratory or series of laboratories. According to my own conception of efficiency in the science of medicine, the whole hospital is the laboratory and every worker in the hospital is a laboratory worker. Personally, I would not work in a laboratory for the study of the ills of man which did not include the whole hospital, to all parts of which I had access. This does

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not mean that the one in charge of laboratories should desire or expect to dominate or in any way control all the departments of the hospital, but it does mean that only by such breadth of vision can one fully appreciate our problem, although each one of us may be especially active only in one phase of the big problem.

A few years ago and, perhaps, even to-day in some hospitals, the word laboratory conveyed and conveys the idea of nothing more extensive than a small room, usually in the basement, for the examination of urine, or perhaps a place where some curious intern might stain bacteria.

In some hospitals, as we progressed, the term became more extensive and was associated with a small, usually the smallest, room somewhere in the morgue. This was the pathologic laboratory. It was a kind of customs house, where the last examination of earthly belongings was made preparatory to sending the body on its long journey back to earth.

From such humble surroundings there soon evolved a building known as the pathologic laboratory. This still remained some distance from the main hospital and always contained the morgue. It was a kind of gate between the physician and the undertaker.

I have always believed that this association with death takes the initiative of life out of many a good scientist.

All these conditions are changing; here and there throughout the hospital one finds to-day rooms equipped with various kinds of apparatus—apparatus for the purpose of studying the living, not the dead. The methods and value of the laboratories have not only invaded the whole hospital, but have invaded every branch of human welfare. Laboratory workers are becoming clinicians who are specializing in the utilization of certain apparatus for the purpose of preventing, curing, and ameliorating the ills of their fellow-man. They are already an economic factor in the progress of mankind. I may not here enumerate statistically all the laboratory activities of man and their value as such a factor.

In the practical hospital which administers to the immediate demands of masses of people the functions and values of laboratories may be summarized briefly:

1. The determination of causes of death (the actual cause being often clinically unknown).

2. Assistance in the making of premortem diagnosis by means of extensive examinations of urine, sputum, blood, stools, excretions, secretions, and tissues microscopically, bacteriologically, physically, and chemically.

3. The actual making of premortem diagnoses, such as result from examinations of neoplasms, and the determination of types of diseases from bacteriologic examination and metabolic status.

4. The determination of the extent of therapeutic procedure by means of examination of urine and blood, feces, sputum, and metabolic status during course of treatment.

5. Prevention of disease by vaccination against small-pox, typhoid fever, tetanus, diphtheria, cholera, etc.

6. The obtaining of prognostic data by determination of probable duration of life, depending on microscopic evidence of malignancy or benignancy of neoplasms and character of metabolic condition.

One of the essentials of our definition of a laboratory consists of the term "apparatus." This term is so broad that it includes everything from the finest microscope or most accurate chemical balance to the most insignificant article in a diet kitchen. There is no place to draw a line. Therefore, I say again, that the whole hospital is the laboratory, or a series of laboratories.

In carrying out the six functions which have just been mentioned the instrument which we call a microscope has played a most important rôle—so important that most laboratories and laboratory workers are usually associated with it. It is only one of many, but its importance may be seen in the fact that during the month of July in our clinic there were 7706 absolutely necessary microscopic diagnoses made on the 4752 patients who were registered during that month. This is almost two examinations for every patient. Of this number of patients there were 4.3 per cent which required a microscopic tissue examination in order to establish a positive diagnosis. Of 1699 patients who came to operation during that month, 61 per cent produced surgical specimens, 20 per cent of which required a necessary microscopic tissue diagnosis.

It might be stated here that the clinician has a percentage of diagnostic accuracy when he makes a positive diagnosis of 95 per cent. As a matter of fact, however, 22.6 per cent of the cancers of the breast which pass through his hands are discovered positively in the surgical laboratory. If our clinicians make a diagnosis of carcinoma (?) or inflammation (?) in the breast they will be correct in only 49 per cent.

These figures, startling as they are, compare favorably with the results in other organs of the body and serve to prove the necessity for immediate tissue diagnosis in connection with surgical procedure unless the surgeon wants to submit his patient to two operations, which doubles

the surgical risk, or take a chance on his ability to diagnose tissues grossly. If he does the latter, he is assuming a proficiency in tissue diagnosis which statistically he has no right to assume, and is submitting his patients to the ravages of his own conceit or ignorance. In the laboratory of surgical pathology in our clinic men who have spent their lives doing nothing else but examining and studying tissues grossly and microscopically in their relation to the patient under the most favorable circumstances must of necessity examine over 20 per cent under the microscope before a positive diagnosis can be made.

These figures represent the efficiency which has followed a careful whole-time study of over 100,000 surgical specimens during a period of training with the microscope of twenty-four years. Perhaps interns today, whose opinions are relied on in many hospitals for tissue diagnosis, belong to a race of supermen. If they do they soon fall from that mighty position when in the environment of ordinary men who have had large experience. The mistakes of these well-meaning and conscientious young men should not be counted against them. The fault rests on the youthfulness of the system of medical science which you and I have had as part of our inheritance. We were born too soon. We were born at the period of transition of medicine from an art to a science, and such transitional periods in nature are usually filled with mistakes.

Great laboratory leaders in this period have been busy discovering and establishing new principles. They have been too busy to associate with the details of clinical medicine. Great physicians, on the other hand, have been too busy administering to the immediate sufferings of humanity to spend time in laboratories. Such isolation at this stage of our development, associated with the duties of teaching students, has been largely responsible for the slowness of coöperation of laboratory methods and facts with clinical methods and facts.

There is one other factor which I hesitate to mention, but the good of humanity demands that some of the more fortunate of us not only mention it, but clearly state the facts for the benefit, not of ourselves, but of others.

The question of compensation for laboratory workers is a vital one, so much so that there is a great and almost disastrous dearth of well-trained laboratory experts. They are not being made, for the simple reason that young men must live and allow their families to live social lives commensurate with their intellectual training. Money, I am thankful to say, has never been the desire of the medical profession, but

if the practitioners of medicine continue to look upon laboratory functions as being in no way equal to their functions in rendering service, the medical profession will either become purely commercial or it will be threatened by the same conquest which now threatens the social world as a whole in the establishment of social justice to all.

It behooves leaders of both purely clinical and laboratory methods of rendering service to coöperate not only in their services, but also in their compensation, whatever that compensation may be. This can be done throughout the medical profession. It is being done by some leaders in a just, honorable, equitable, ethical, and gentlemanly manner to the satisfaction of all parties, especially the patient, who reaps the reward of the highest type of efficiency.

What I have said briefly and very generally so far is in the nature of destructive and constructive analysis.

From a purely constructive standpoint time permits only certain suggestions which are derived from some isolated experiments which have been carried out successfully in a few hospitals with which I am personally acquainted. The experimental stage is past and it only remains for us to summarize the generalizations.

1. Some leaders in the medical profession have selected young men who have manifested natural inclination and capacity for laboratory methods of investigation from research and clinical standpoints and encouraged them by opportunities and just earthly compensation. As a result these young men are enthusiastically striving to advance and are actually advancing the science of medicine along all lines for the sake of humanity.

2. Some trustees of hospitals with which I am acquainted have been successful and efficient business men from the standpoint of methods, and some of these business men are realizing that human progress is dependent absolutely on the health and happiness of mankind. Such men are, by constructive and efficient methods, organizing hospitals for the science of medicine, fully equipped structurally and functionally for efficient service in all branches which are productive of efficiency.

3. Some laboratory experts are beginning to statistically prove the inefficiency of some of our old methods and the efficiency of newer methods of intimate coöperation of departmental science in the practice of medicine in hospitals.

4. The general public is beginning to demand laboratory examinations, a fact which is evidence that the layman has begun to learn that

the practitioners of medicine must be something more than the possessors of a pleasant personality and a capacity to arouse blind faith.

In conclusion I wish merely to state that as one trained in laboratory methods and intimately in association with clinical medicine, I am convinced that no hospital has reached the highest efficiency which has not coördinated the best laboratory methods with its rendition of service to its patients, and that no practitioner can render the most efficient service who does not call laboratory methods into consultation.

Unfortunately, we have not enough well-trained laboratory men, but they can be made only by your recognition of their value and your material and moral assistance.

I regret that time does not permit me to present to you the vast statistics which I have at my disposal to prove accurately the relationship which does exist in some hospitals and must soon exist in all hospitals.

My mission at this time is one only of stimulation. You who are eager to render the best services will look for the statistics. Your presence here has already proved your desire for improvement. You are ready for the big conception that this is not only a day of specialization, but a day of the coördination of specialization for the cure, amelioration, and prevention of disease, and this coördination can be carried out only in hospitals, which I still contend are nothing but laboratories.

Now, let me answer from experience the questions, "Who should direct them?" and "Who should do the technical work?"

True science knows only the greatest efficiency as a goal, and the greatest efficiency in laboratory direction is not confined to any sex, race or religion. It deals largely with the personal equation of accuracy of observation, correlation, and generalization.

It is logical to suppose that an individual who has been especially trained and has had a large experience might render greater service than the untrained and inexperienced. It is also logical to suppose that any individual who devotes his whole time to a subject will in the same number of days be more efficient. It takes time to train, and time and experience travel in parallel lines. It seems logical to suppose that an individual who has experience and is trained would make a more efficient director than the inexperienced or partially experienced, untrained or partially trained individual. Since laboratory methods are becoming more numerous and are changing and the facts are rapidly increasing

there is no individual who is trained completely. It is purely a relative matter.

My advice is simply this: Obtain for your hospital the best trained and the most experienced young man or woman who has great possibilities of growth. Never take a finished product. I have a suspicion from the subject presented to me that you really want to know if your laboratory director or worker should be a practitioner, and my answer is only as a consultant.

The question of who should do the technical work is a matter to be dealt with just as was the director. Any individual who is physically and mentally fit can do any technical work in any laboratory. In our own laboratories we have girls and boys as technicians. There is absolutely no reason why Sisters cannot do the technical work of a laboratory just as well as they do the numerous other important technical things which make a hospital a success.

In conclusion, allow me to express publicly our great appreciation of our own good Sisters, led by Sister Mary Joseph, who have at all times heartily coöperated in every possible way in our efforts to best serve humanity.

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